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VOLUME 46

1930

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JULY, 1930

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois. Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized June 14, 1918.

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Archives of Internal Medicine

VOLUME 46 JULY, 1930 NUMBER 1

FREQUENT CHEST COLDS

VARIABILITY IN THEIR OCCURRENCE AND THE BACTERIOLOGY IN THOSE VERY SUSCEPTIBLE TO THIS TYPE OF COLD *

I. CHANDLER WALKER, M.D.
AND
JUNE ADKINSON, A.M.
BOSTON

This paper concerns only persons who were accustomed to have three or more chest colds a year for a number of years, and who were observed at the time of the colds. Data for thirty-one patients are presented in table 1 to illustrate the variability in the occurrence of colds. Of this number, seventeen were normal persons, and the remaining fourteen were subject to asthma when they had a cold. In fifteen of the thirty-one patients, frequent bacteriologic examinations of the sputum were made at the time of a cold in the chest. Eight of this group were normal persons and seven had asthma with their colds; these cases are presented in table 2. All of the thirty-one patients, whether or not they had asthma, were free from symptoms in the interim between the colds in the chest; therefore, so far as this paper is concerned, all might be considered as normal persons who were subject to frequent chest colds.

The bacteriologic examination, stated briefly, was as follows:

Washed masses of thick sputum, which was raised in the early morning and collected in sterile bottles, were shaken in dextrose bouillon and then inoculated into human blood agar which was poured into petri dishes. After the blood agar plates were incubated from twenty-four to thirty-six hours, depending on how rapidly growth took place, they were examined for types of colonies. Numerous colonies were picked off, inoculated into tubes of dextrose bouillon and incubated for twenty-four hours. These bouillon cultures were then examined for different organisms, and those containing streptococci were inoculated into litmus serum waters. Therefore, examination of the blood agar plate revealed the presence or absence of pigment and hemolysis for the various colonies; examination of the dextrose bouillon culture determined the morphology and straining reaction of the organisms, and the litmus serum waters in the case of the streptococci differentiated both the hemolytic and the nonhemolytic strains into eight subgroups or varieties. No attempt was made to identify bacilli except for morphology, pigment, motility

* Submitted for publication, Nov. 25, 1929.

* The patients were observed in private practice; the bacteriologic work was done in the Medical Laboratory of the Peter Bent Brigham Hospital.

and staining characteristics. For a more detailed description of the bacteriologic technic, reference may be made to a previous paper.[1]

EXPERIMENTAL DATA

In the first column of table 1, a number represents a patient; in the second column, the letter *N* stands for a normal person who had chest colds, and the letter *A* means that the patient had asthma with the chest colds. The remaining columns are headed by figures which denote the various years during which the patient was under observation, and the figures separated by dashes in these columns represent the months

TABLE 1.—*Variability of the Occurrence of Colds in Thirty-One Patients*

Patient		1923	1924	1925	1926	1927	1928	1929
1	N	4-10-12	2-4-9-11	2-9-12	3-9-12	4-10-12	1-5-9-12	.....
2	A	3-10-12	2-10-11	2*-10-12	1-3-5-9	3-9-11	4-9-11	3
3	N	1-2-3-5-12	2-5-7-11	1-3-9-12	1-3-5-11-12	1-3-5-10-12	*	.....
4	A	3-9-11	4-9-12	3-8-10	11*	4-7-9-12	2-9-12	3-6
5	N	1-3-6-10	2-4-7-11	3-5-6-10	1-4-8-12	.....	.....	.....
6	N	2-8-10	2-5-9-11	2-8-11	.....	.....	.....	.....
7	A	2-4-11	1-4-10	6*	9*	*	1*	.....
8	N	3-4-9-11	1*	2*	1-3-5-9	*	3-5-10	.....
9	N	10*	3-4-5-11	9*	11*	3*	4-10-11	1-3
10	N	.....	.....	1-6-8	1-5-10	5*	3*	.....
11	N	.....	.....	3-6-12	3-6-9	*	2-6-7-9	*
12	A	.....	.....	.....	2-4-10-12	3-5-7-9-12	3-7-9-12	3-5
13	N	.....	.....	.....	1-4-9-11	1-5-7-9	1-2-4-9-12	2*
14	A	.....	.....	.....	3-6-9	3-6-12	1-7-10	1*-6
15	A	.....	.....	.....	1-3-10-12	1-4-9-11	3-6-9-11	*
16	A	.....	.....	.....	6-8-10	1-4-9	1-2-3	*
17	N	.....	.....	.....	1-2-3-11	1-9-11	1-2-3-9	1-3
18	N	.....	.....	.....	3-10-12	3-9-10-12	3-6-9	1-4-6
19	N	.....	.....	.....	4-9-11	1-3-12	3-9-10-12	1*
20	A	.....	.....	.....	1-3-8-10	3-4-9	*	.....
21	A	.....	.....	.....	.....	2-5-8-10	1-2-6-9-11	3*
22	A	.....	.....	.....	.....	1-3-10	1-3-9-11-12	1-3-6
23	A	.....	.....	.....	.....	2-7-11	2-3-9-11	*
24	N	.....	.....	.....	.....	2-4-9-11	1-2-5-9-12	1-5-7
25	A	.....	.....	.....	.....	3-5-10-12	3-5-10-12	3*
26	A	.....	.....	.....	.....	1-2-7-10	1-3-9-10	*
27	N	.....	.....	.....	.....	2-6-9-11	9*	1*
28	N	.....	.....	.....	.....	.....	1-7-9-10	1-4-6
29	A	.....	.....	.....	.....	.....	2-4-10-11-12	3-4-6
30	N	.....	.....	.....	.....	.....	3-5-9-10-12	1-4-7
31	N	.....	.....	.....	.....	.....	2-7-10	4*

when the patient had a cold; for example, the figure 1 stands for January, 2 for February, 3 for March and so on. The asterisk (*) means that the patient was given preventive treatment against colds during that year.

There would seem to be no need for lengthy discussion of table 1, as all necessary data are presented in it. The first three patients may be taken as an example of all the others. Patient 1, a middle-aged man, was observed for six years, during which time he had twenty colds; there were three colds during each of four years and four colds during each of the other two years. He had a cold in December in

1. Walker, I. Chandler, and Adkinson, June: Bacteriologic Examination of Seven Hundred and Twenty-Four Sputums from as Many Patients with Bronchial Asthma, Arch. Int. Med. **41**:601 (April) 1928.

five of the six years, a cold in September in four of the six years, no cold in June, July or August, and in the other months he had a cold in only one or two years. Patient 2 was a middle-aged woman who had asthma when she had a cold. She had nineteen colds during the six years that she was under observation. During three years she had a cold in each of the months of September, October, November and March; she had no colds in June, July or August, and during one or two years, she had a cold in each of the remaining months. Patient 3, a middle-aged woman, had twenty-three colds in five years. During four years she had colds in each of the months of January, March, May and December; in April, June and August she had no colds, and in the other months she had only one or two colds.

The three patients mentioned lived in the same community; the first and third patients were brother and sister; the second and third were both school teachers; all were practically the same age. The first patient was especially prone to colds during the months of September and December, and the second patient during the months of September, October, November and March; the third patient had most of her colds in January, March, May and December. The first two patients had no colds in June, July and August, and the third patient had one cold in July, but none in April, June or August. In contrast to these three patients, who rarely had colds during the summer months, patients 11 and 14 had colds for several years in June and once in July, and numerous other patients, it is noted, had colds in June, July or August. In other words, some persons who are prone to colds are more apt to have a cold in certain months year after year, other persons have more colds in some other months and still others are more prone to colds in months that are different from either of these. Since all of the thirty-one patients lived within a ten mile radius of Boston, climate, changes in weather, epidemics and exposures would be approximately the same for all in each month. Therefore, the incidence of colds in these cases cannot be correlated very well with these extraneous conditions.

During 1923, eight patients had a total of twenty-eight colds; during 1924, eight patients had the same number of colds, and during 1925 eight patients had two less, so that the same number of patients had practically the same number of colds in each of the three years. During January, May, June, July and August for all three years there was the least number of colds; a total of five colds in any of these months for the three year period was the maximum. Of the other months, during February, March and November there was the largest number of colds, and the months of October and December were a close second, while the months of April and September were next in point of frequency. During 1926, twice as many patients had twice

the number of colds. During this year, January and March were the most popular months for colds; September, October and December were the next most popular, but the ratio was nine for the former to six for the latter. During February and the summer months, there was the least number of colds. During 1927, twenty patients had a total of seventy-two colds, and the frequency per month was practically the same as in the previous year, with the exception that September was the leader in frequency. During 1928, twenty-four patients had a total of eighty-eight colds, and again the month of September led in frequency, and January, March, October and December were second in frequency.

On the percentage basis, March led in the frequency of colds; it was among the leaders in frequency for five years. January was among the leaders in three years, February and September in two years and April, October, November and December in one year. January, March and September were most consistent in frequency of colds. It is readily seen, however, that there was wide variance among the months for different years as regards the frequency of colds. In other words, the month of the year had little bearing in general on the frequency of colds, with the exception that during September to May, inclusive, chest colds were more frequent than during the summer period.

The prevalence of epidemics of colds seems to have little bearing on the incidence of chest colds in those very susceptible. Every year during September, when the days are very warm and the nights are frosty in Massachusetts, a large number of colds occur; yet in the cases reported, only in the years 1927 and 1928 did these patients have an unusual number of chest colds. During the past winter, there was an epidemic of colds and influenza in Massachusetts from the middle of December to the middle of January. This group of patients, however, had no greater number of chest colds in December than in the previous January, March and October, nor as many as in the previous September. Furthermore, in January during the epidemic there was no greater number of chest colds in this group than in the following March, and there were fewer colds than in the previous months of January, March, September, October and December. Again the total number of chest colds in this group of cases for December and January, when there was a recognized epidemic, was eighteen, whereas in the previous December and January there was a total of seventeen when there was no general epidemic. Therefore, the presence of epidemics of colds and upper respiratory infections seems to play no part in the incidence of chest colds in very susceptible persons.

It is of interest to consider the incidence of chest colds in this group of cases during the months when there is the least sunshine. March led in the frequency of chest colds in five of the six years under consider-

ation. During January, a sunless month, there were many chest colds in three years, but in no year was there a larger number of colds than in March of the same year, when there is a good deal of sunlight. February, a month of cold weather and little sun, in comparison, accounted for fewer colds than September, a month of more sun and milder weather. In the month of December, when there is the least sun and much cold, in only one year (1928) was there any appreciable increase in the frequency of chest colds, and even in this instance no more colds were recorded than in January, March, September and October of the same year. During the six years there were nearly as many chest colds in May as in November; yet there is a marked difference in the amount of sun and the degree of cold in these two months. Therefore, with the exception of the months of July and August, when there were very few colds, and of June, when there were fewer colds than during the remainder of the year, the frequency of chest colds in this group of cases cannot be correlated with the absence of sunshine.

The same conclusion is reached if the months of the six year period are grouped according to sunlight. During the months of August, September and October, a total of eighty-one colds was recorded; during the months of November, December and January, there were eighty-eight colds; during the months of February, March and April there were eighty-four colds and during the months of May, June and July there were only forty-four colds. By grouping September, October, March and April together, there is a total of 121 colds, in comparison to 113 colds by grouping together the months of November, December, January and February for the six years.

Consideration of the interval of freedom between colds may throw some light on the cause of frequent colds in the very susceptible person. Excluding the summer period, from June to August inclusive, during which time, as already noted, most patients are free from colds, there were 251 intervals between colds in all of the 31 patients presented in table 1. Of this number, there were forty-two, or nearly 17 per cent, intervals of one month; ninety-two, or 36.5 per cent, intervals of two months; sixty-six, or 26 per cent, intervals of three months; twenty-three, or 9 per cent, intervals of four months, and twenty-eight, or 11 per cent, intervals of five or more months of freedom between colds. In other words, in more than a third of the instances a chest cold occurred two months after the preceding chest cold; and in more than another fourth of the instances a chest cold followed the preceding one in three months; in about one sixth of the instances there was only one month between colds; in less than one tenth of all the interval was four months, and in slightly more than a tenth the total was five or more months.

In other words, in nearly two thirds of the instances, patients had a cold two or three months after the preceding cold, and in another one sixth the interval was one month. Therefore, as regards the patient, in these cases the immunity established by a chest cold was of short duration. From the standpoint of bacteriology, the cold-causing organisms may be so numerous that some of them cause one cold and others cause the next cold and still others a succeeding cold, so that the frequency of chest colds might be due to these several organisms acting independently and each producing immunity for itself but not for the others rather than from lack of immunity to the same one or more organisms that caused every cold.

Some of these patients were given a curative dose of mixed streptococcus vaccine, as reported in a former paper,[2] on the second day of their cold, and this treatment seemed to be of benefit in that the cold often rapidly improved and usually disappeared within from one to three days. In other patients, the curative vaccine did not give benefit, and the chest cold continued for two or three weeks. In still others, the chest cold was present for one or two weeks before the curative vaccine was given. As careful a checkup as it is possible to make showed that in these patients the interval of freedom between colds did not seem to be modified whether the patient's cold was of short or of long duration, or whether the patient was treated early or not at all during the cold.

Attention might be directed, incidentally, to those patients who in some years (as evidenced by an asterisk) were given preventive treatment with mixed streptococcus vaccine as already described in a previous paper.[3] Exclusive of the year 1929, which was only half finished at the time this article was written, during three yearly periods there were no colds in patients who were accustomed to have three colds a year; in thirteen periods of a year the usual number of three colds was reduced to one, and in four yearly periods the usual number of four or five colds was reduced to one. The year 1929 would seem to bear out similar or better results, since in the period from January to June, inclusive, in five instances in which the usual number of colds had been three or more, there were no colds, and in six other instances the usual number of three or more colds was reduced to one.

In the first column of table 2, the patient is distinguished by a number which refers to the same patient in both tables; in the second column, the letters *N* and *A* refer to the same as in table 1. The third

2. Walker, I. Chandler: Colds and Asthma Associated with Colds: Preventive Treatment with Vaccines, Arch. Int. Med. **43**:429 (April) 1929.

3. Walker, I. Chandler: The Curative and Possibly Specific Effect upon Colds of Vaccines Consisting of the Streptococci Prevalent During that Period, Am. J. M. Sc. **178**:645 (Nov.) 1929.

column gives the year and the fourth column the month of that year in which a bacteriologic examination of the sputum was made at the time of a cold. In the fifth column, the type of predominating organism is noted; the letters *N.H.* refer to nonhemolytic and the letter *H.* to hemolytic, while the letter *E.* means that both nonhemolytic and hemolytic types of colonies were approximately equal in number. The next eight columns are headed by the names of the eight varieties of hemolytic streptococci, and the second group of eight columns by the names of the eight varieties of nonhemolytic streptococci; the plus sign (+) in these columns means that that variety of streptococcus was recovered from the sputum. Another column is set aside for *Staphylococcus pyogenes-aureus,* and another for bacilli. The last column, which is headed by "Comments," contains several symbols, which are explained as follows. The letter *X* means that only one type of organism, as noted in the table, grew on the agar plate; the letter *Y* means that a few hemolytic colonies were present in the plate but that they did not grow in transplant, and the letter *Z* means that a few nonhemolytic colonies were present in the plate but they did not grow on transplant. Therefore, in these instances these varieties of hemolytic and nonhemolytic organisms could not be identified. The letter *T.* refers to *Micrococcus tetragenus;* the letter *S.* stands for *Sarcinae;* the letters *S.C.* mean *Staphylococcus pyogenes-citreus,* and *S.A.* means *Staphylococcus pyogenes-albus.*

The observations in table 2 are so evident that detailed discussion of all of the patients is unnecessary; a discussion of one patient will suffice. Bacteriologic examination was made of the sputum of patient 17 in 1926, when he had three colds during the three successive months of January, February and March, and with each cold a different type of streptococcus was recovered from the sputum. Eight months later, in November, a still different variety of streptococcus was found. In none of the four examinations was the same variety found twice. From September, 1927, to March, 1928, inclusive, examinations of the sputum were made at the time of five colds. In four successive sputums, nonhemolytic *Streptococcus ignavus* was recovered and in three sputums hemolytic *Streptococcus anginosus,* but four other varieties of streptococci that were found on the first examination were not found subsequently, and in one sputum *Staphylococcus pyogenes-aureus* was recovered. Six months later five varieties of streptococci were recovered, one of which was present six months previously; another was present nearly two years previously and a third was present seven months previously, but the other two varieties had not been recovered before. In January, 1929, or four months after the previous examination, two varieties of streptococci, which were recovered, were present four months previously; another was recovered nearly three years

TABLE 2.—*Results of Bacteriologic Examinations of the Sputum in Fifteen of the Thirty-One Patients*

Patient	Year	Month	Predominating Organism	Hemolytic Types								Nonhemolytic Types										
				Subacidus	Anginosus	Pyogenes	Infrequens	Equi	Hemolyticus Type I	Hemolyticus Type II	Hemolyticus Type III	Ignavus	Salivarius	Fecalis	Mitis	Equinus	Nonhemolyticus Type I	Nonhemolyticus Type II	Nonhemolyticus Type III	Staphylococcus Pyogenes-Aureus	Bacillus	Comments
17 N	1926	Jan.	N. H.	+	..	..	..	..	..	..	..	+	..	..	..	..	..	..	+	..	..	...
		Feb.	H.	..	+	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	...
		March	H.	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	..	X
		Nov.	H.	..	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	X
	1927	Sept.	H.	..	+	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	...
		Nov.	N. H.	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	+	..	Y
	1928	Jan.	N. H.	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	X
		Feb.	N. H.	..	+	..	..	..	..	..	..	+	..	+	..	..	..	..	..	..	..	...
		March	N. H.	+	+	..	..	..	..	..	..	+	+	..	..	..	..	..	+	..	..	...
		Sept.	H.	+	..	+	+	..	..	+	..	..	..	+	..	..	..	..	..	..	..	...
	1929	Jan.	N. H.	+	..	+	..	..	..	..	+	..	..	..	..	..	..	..	+	+	..	...
		March	H.	+	+	..	..	..	..	..	+	+	..	..	+	..	..	..	+	..	..	...
18 N	1926	Oct.	E.	+	..	..	..	+	..	..	..	+	..	..	..	+	..	..	..	..	..	...
		Dec.	N. H.	..	..	..	..	..	..	..	..	..	+	..	..	..	+	..	..	..	..	X
	1927	March	E.	+	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	...
		Sept.	N. H.	+	..	..	..	..	..	..	..	+	+	..	..	..	..	..	..	..	..	...
		Oct.	H.	+	..	..	..	..	..	..	..	+	..	..	..	..	+	..	..	+	..	...
		Dec.	N. H.	..	..	..	..	..	..	..	..	+	..	+	..	..	+	..	..	..	..	Y
	1928	June	N. H.	+	..	+	..	..	..	..	+	..	..	+	..	..	..	..	..	..	..	...
		Sept.	H.	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Z
	1929	Jan.	N. H.	..	..	..	..	..	..	..	..	..	+	..	+	+	..	..	..	..	..	Y
		April	N. H.	+	+	+	..	+	..	..	..	+	..	..	+	..	..	..	..	..	..	...
		May	H.	..	+	..	..	..	..	..	..	+	..	..	+	+	..	..	+	..	..	...
22 A	1927	March	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	X
		Oct.	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	X
1 ..	1928	Sept.	H.	+	..	..	+	+	..	..	..	..	..	..	..	..	..	..	..	..	..	Z
		Nov.	N. H.	..	..	..	..	..	+	+	..	..	..	+	..	..	..	..	..	..	..	...
		Dec.	E.	..	+	..	..	..	+	..	..	..	..	..	..	..	+	..	..	..	..	...
	1929	Jan.	H.	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	..	..	..	Z
		March	N. H.	..	..	..	..	..	..	..	..	+	..	..	..	+	..	..	..	..	..	X
24 N	1927	Sept.	H.	..	..	..	..	..	+	..	..	+	..	..	..	..	+	..	..	..	..	...
		Nov.	N. H.	+	..	+	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	...
	1928	Jan.	N. H.	..	..	..	..	..	+	..	+	..	..	..	..	..	+	..	..	..	..	...
		Feb.	N. H.	+	+	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	...
		May	N. H.	+	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	...
		Sept.	H.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Y
		Dec.	H.	..	+	..	..	+	..	..	..	..	..	..	..	+	..	..	..	+	..	...
	1929	Jan.	H.	+	..	+	..	+	..	..	..	+	..	..	..	..	..	..	+	..	..	...
29 A	1928	Oct.	H.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Y
		Nov.	H.	..	+	+	..	.	+	..	..	+	..	..	..	..	..	..	..	..	..	T.S.
		Dec.	N. H.	..	..	..	+	..	..	+	..	..	..	+	..	+	..	+	..	..	..	S.C.
	1929	March	H.	+	+	..	..	+	..	..	..	..	..	..	..	..	..	..	+	..	..	...
19 N	1928	Jan.	E.	..	..	..	..	..	+	..	..	..	..	..	..	..	+	..	..	..	..	...
		Sept.	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	X
		Oct.	H.	..	..	..	+	+	..	+	..	..	..	..	..	+	..	..	..	..	..	...
	1929	Jan.	N. H.	..	+	..	..	..	..	..	..	..	+	..	..	+	..	..	..	..	..	...

TABLE 2.—*Results of Bacteriologic Examinations of the Sputum in Fifteen of the Thirty-One Patients—Continued*

Patient		Year	Month	Predominating Organism	Hemolytic Types									Nonhemolytic Types										
					Subacidus	Anginosus	Pyogenes	Infrequens	Equi	Hemolyticus Type I	Hemolyticus Type II	Hemolyticus Type III		Ignavus	Salivarius	Fecalis	Mitis	Equinus	Nonhemolyticus Type I	Nonhemolyticus Type II	Nonhemolyticus Type III	Staphylococcus Pyogenes-Aureus	Bacillus	Comments
30	N	1928	Sept.	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	X
			Oct.	N. H.	..	+	..	..	..	..	..	..	..	+	..	..	+	..	..	..	..	..	+	..	X
			Dec.	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	Y
		1929	Feb.	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	Y
28	N	1928	Jan.	N. H.	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	+	..	+	X
			Sept.	N. H.	..	..	..	..	..	+	..	..	..	+	..	+	..	..	..	..	..	+	+	..	S.A.
		1929	Jan.	N. H.	..	..	..	..	..	..	..	..	..	+	..	..	+	..	..	..	..	..	+	X
			April	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	...
23	A	1927	Nov.	N. H.	..	..	..	+	..	+	..	..	..	..	..	..	..	..	..	..	..	..	+	..	...
		1928	Feb.	H.	..	+	..	+	..	..	..	..	..	+	..	+	..	..	..	..	..	..	+	...
			March	H.	..	..	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	X	
			Nov.	N. H.	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	X	
31	N	1928	Feb.	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	+	...	
			July	N. H.	..	..	..	+	..	..	..	..	..	..	..	+	..	..	+	..	..	..	..	S.C.	
			Oct.	N. H.	..	+	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	+	...	
		1929	April	H.	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	...	
25	A	1927	Oct.	H.	+	+	..	..	..	..	..	..	..	+	+	..	..	..	..	..	..	..	..	...	
			Dec.	N. H.	..	+	..	..	..	..	..	..	..	..	+	..	+	..	..	..	..	..	+	X	
		1928	May	E.	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	...	
			Oct.	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	X	
		1929	March	H.	+	+	..	+	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	...	
12	A	1926	Dec.	H.	+	..	..	..	..	+	..	..	..	..	..	+	..	..	+	..	..	..	..	..	...
		1927	May	N. H.	+	..	..	..	..	..	..	..	..	..	+	..	+	+	..	..	..	+	..	...	
			Sept.	H.	..	+	+	..	..	+	..	..	..	+	..	..	+	..	..	..	..	..	+	...	
		1928	Sept.	N. H.	..	+	+	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	...	
			Dec.	E.	+	+	..	..	..	+	..	..	..	..	+	+	..	..	+	..	..	..	..	...	
21	A	1927	Oct.	H.	+	..	..	+	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	...	
		1928	June	N. H.	+	..	..	+	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	Y	
			Sept.	N. H.	..	..	..	..	..	..	..	..	..	+	..	..	..	..	+	..	..	+	+	X	
		1929	March	N. H.	..	..	.	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	...	
26	A	1927	Oct.	E.	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	...	
		1928	Jan.	N. H.	..	..	..	..	..	..	+	..	..	+	..	..	..	..	+	..	..	..	..	X	
			Oct.	N. H.	..	..	..	..	..	..	..	..	..	+	..	..	..	..	+	..	..	..	..	...	
10	N	1928	Oct.	H.	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	...	
			Nov.	N. H.	..	..	..	..	..	..	..	..	..	+	+	..	..	..	..	..	..	..	..	Y	
		1929	Jan.	N. H.	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	Y	

before; another was the same as one found nine months previously, and a fifth variety that had not been found previously was recovered. Three months later five varieties of streptococci that had been recovered at some previous time were present and also still another variety that had not been previously recovered. In the four last examinations *Streptococcus hemolyticus-subacidus* was recovered each time, and three other varieties were found repeated once in successive sputums, but of the other varieties that were repeated there were long intervals and one or more colds between repetitions.

During the last two and one-half years, bacteriologic examination of the sputum of patient 17 was made twelve times. The predominating organisms were equally divided between the hemolytic and the nonhemolytic types; in four successive instances each type predominated; in two sputums hemolytic types of streptococci were the only organisms present; in one instance the nonhemolytic type was present alone, and in one specimen, in which both types of colonies were present on the agar plate, no hemolytic colonies grew in subculture. With the exception of one sputum which grew *Staphylococcus pyogenes-aureus* in addition to streptococci, no organism other than streptococci was recovered. In six sputums *Streptococcus ignavus* was recovered; in five sputums, *S. subacidus* and *anginosus;* in four sputums, *nonhemolyticus* type III, and in three sputums, *pyogenes, hemolyticus* type III and *salivarius. Streptococcus equi, hemolyticus* type I, *equinus* and *nonhemolyticus* type I were not found, and the other four varieties were recovered from one sputum.

From one sputum six varieties of streptococci were recovered; from three sputums, five varieties; from two sputums, three varieties, and from the other six sputums, only one or two varieties of streptococci.

Therefore, there is great variability in the types of streptococci that are present in the sputums of patients with chest colds, whether the colds occur at intervals of one or several months. Four or five varieties of streptococci are apt to be present more frequently than some other varieties, provided numerous sputums are examined over a long period of time, but in the same length of time most of the other varieties will be present one or more times. If examinations are confined to some one year or to one or two sputums a year for two or three years, entirely different varieties of streptococci may predominate. For instance, with patient 17 the percentage prevalence of streptococci in the four sputums taken in 1926 is different from that found in the four sputums taken in 1928, and some of the less frequent varieties of streptococci that were present in 1926 were absent in 1928 and vice versa.

Consideration of table 2 as a whole is of interest. Eighty-two bacteriologic examinations were made of as many sputums from the fifteen

patients during the two and one-half year period. At least two examinations were made a year of sputum from each patient; in four instances four examinations were made in one year, and in seven instances three examinations were made. From the standpoint of successive examinations, in many instances four and five examinations were made during a seven or eight months' period. In forty-seven examinations nonhemolytic colonies predominated; in twenty-eight examinations hemolytic colonies predominated, and in seven examinations these two types were approximately equal. In only four instances were streptococci not present.

Consideration of the columns headed *Staphylococcus pyogenes-aureus*, Bacilli and "Comments" reveals the following facts. Referring to the letter *X*, nonhemolytic colonies only were present in fourteen examinations and hemolytic colonies only in two sputums. The letter *Y* reveals that in eight sputums a few hemolytic colonies were present with many nonhemolytic colonies, but the hemolytic colonies failed to grow in subculture and were therefore not classified. In two sputums both types of colonies were present but failed to grow in subculture. Reference to the letter *Z* reveals that in three sputums a few nonhemolytic colonies were present together with numerous hemolytic colonies, but in subculture these nonhemolytic organisms did not grow and consequently were not classified. In four sputums from which nonhemolytic colonies only were grown no streptococci were recovered; in two of these sputums, only *Staphylococcus pyogenes-aureus* was recovered, in one only bacilli and in the third both *Staphylococcus pyogenes-aureus* and bacilli.

Of the eighty-two sputums that were plated, in only nine was *Staphylococcus pyogenes-aureus* recovered, in another *Staphylococcus pyogenes-albus*, in two others *Staphylococcus pyogenes-citreus*, in one both *Micrococcus tetragenus* and *sarcinae* and in twelve bacilli. These statistics take into consideration only those plates from which contamination seemed to be eliminated. Naturally, sometimes duplicate plates that were obviously contaminated by bacilli, *Staphylococcus pyogenes-albus* or air organisms were eliminated. Although the types of bacilli were not identified, sufficient study was given to them to determine that none of them were *B. pyocyaneus, B. Friedlander, B. typhosus, B. coli-communis* or *B. subtilis*. It is of interest to note the rare occurrence of the common types of staphylococci, with the exception of *Staphylococcus pyogenes-aureus*, and of the common types of micrococci and diplococci which are supposed normally to frequent the upper respiratory tract.

In comparing the examinations of the first four patients with those of the other patients, the absence of bacilli and of all organisms other than streptococci is noted in the former. This is probably due to the

fact that with the first four patients the specimens of sputum were cultivated within three or four hours after being raised, and the patients were careful about collecting the specimens. The other patients were of the average type and not so particular about the specimens, and often the specimens, although kept cool, were not plated for twenty-four hours.

Variability is noted among the varieties of streptococci in sputums taken from all of the patients collectively during the period of a year or more. By comparison of the more frequently recovered varieties for the years 1927 and 1928, it is found that in 1928 the varieties of *subacidus, ignavus* and *salivarius* were recovered much less frequently than in 1927, the variety *infrequens* was much more frequent and the varieties of *anginosus* and nonhemolytic type I were recovered in very nearly the same frequency.

Variability is also noted among the more frequently recovered varieties of streptococci from the individual patient during the period of a year or more. During the period 1926 and 1927, the variety of *subacidus* was recovered once from six sputums of patient 17 and four times in the sputum of patient 18. From seven sputums of patient 22 taken during the years 1927 to 1929, inclusive, *subacidus* was recovered only once, but during the same interval it was recovered four times from the sputum of patient 24. During 1928 and 1929, the same variety of streptococcus was not recovered from four sputums of patients 19, 30, 28 and 23, but it was consistently recovered one or more times from all of the other patients during the same period. The variety *anginosus* was recovered four times from the sputum of patient 17, but not at all from that of patient 18 during the period 1927 to 1929, inclusive. During the period 1926 to 1928, inclusive, the variety *hemolyticus* type I was not recovered from the sputum of patients 17 and 18, but it was recovered from two sputums of patient 22 in 1928. The varieties of *ignavus* and *salivarius* were recovered consistently from some patients, but were not recovered at all from others. During the period 1926 to 1929, inclusive, the variety nonhemolytic type I was not recovered from any of the twelve sputums of patient 17, but during the same period it was recovered from three of eleven sputums of patient 18. Neither was this variety recovered from three other patients, but it was consistently recovered from all of the remaining ten patients.

Variability among the varieties of streptococci recovered from successive sputums obtained from the same patient is similarly noted. First will be discussed those patients whose successive sputums were examined in successive months, and then those whose successive sputum were examined, but in whom a month intervened between colds.

The sputum of patient 17 was examined when he had colds in the successive months of January, February and March in 1926, with the result that of the six varieties of streptococci recovered none occurred

twice. In 1928, similar examinations were made in the same months; the variety *ignavus* was recovered from each of the three sputums, and the variety *anginosus* was recovered in two successive sputums, but the third variety in the second sputum did not repeat, and in the third sputum three varieties that had not been recovered in the previous two sputums were present. The sputum of patient 18 was examined in 1927 in September and October and in 1929 in April and May. In the first pair of examinations, two varieties of streptococci repeated and one did not; in the second two successive months, two varieties of streptococci repeated and five did not. Of the sputum of patient 22, three successive examinations were made in November, December and January, with the result that one variety of four repeated in December and one of three in January; in this case, the same variety repeated both times, so that it was present in all three successive sputums. In January and February of 1928, sputums from patient 24 were examined, and none of the three varieties repeated. The same was true with patients 29 and 30; with the former patient, four varieties were present in November, 1928, and five different varieties were present in December, and with the latter patient, the three varieties of streptococci that were present in October were unlike the one that was recovered the previous September.

In other words, in two instances the same variety of streptococcus was recovered from all three sputums taken in three successive months; in three other instances, the same variety repeated the following month; in another three instances, there were no repetitions in the following month, and in one instance, there were no repetitions when three successive sputums were examined in three successive months. Therefore, without further analysis it would seem that those patients whose sputum contained the same organism in two successive months had a very short duration of immunity to these respective organisms. In all instances but one, however, along with the variety that repeated, there were two and often four other varieties, so that the patient may have had immunity to the recurring organisms even though they were in the sputum, and the colds may actually have been caused by other organisms that had not recently been recovered from the sputum. The fact remains, however, that some patients who are prone to chest colds have the same variety of streptococcus with other varieties in their sputum in successive months, while other patients have several different varieties with each successive monthly cold.

The following instances are those of successive examinations of sputum from colds that occurred at intervals of two months; that is, there was a month of freedom between colds. In 1927, the organism recovered from the sputum of patient 17 in November was different from that recovered in September, but during the next cold in January

the same organism that was present in the sputum in November recurred in January. In 1926, patient 18 had different varieties of streptococci in the sputum in October and in December, but in the same months of 1927 two of the three varieties present in October recurred in December. From the sputum of patient 22, none of the four varieties of streptococci that were recovered in September, 1928, was recovered the following November. From the sputum of patient 24, one of the four varieties of streptococci that were recovered from the sputum in September, 1927, was present in the following November, but two months later, in January, none of the four that were present in November recurred. In the case of patient 30, none of the varieties that were recovered from the sputum in October, 1928, was present in December, and the same was true again in February. In the case of patient 25, two of the four varieties that were recovered in October, 1927, were also recovered the following December. Therefore, the observations in this paragraph very nearly duplicate those of the previous one, and similar conclusions are justified, although there was less repetition and more variability among the varieties of streptococci in succeeding sputums.

The difficulties that obtain in making a mixed vaccine of the varieties of streptococci are evident. A combination of all of the sixteen varieties is impracticable, and a combination of the varieties that are encountered most often would still leave out a number of varieties the total of which would comprise an appreciable percentage of frequency. For instance, in the year 1928 forty-eight strains of hemolytic and a like number of nonhemolytic strains were recovered from thirty-seven sputums from the fifteen patients in table 2. A selection of the most frequent varieties of hemolytic streptococci, namely, *subacidus, anginosus, infrequens* and hemolytic type I would comprise a total of thirty-six of the forty-eight strains that were encountered, and twelve strains distributed among the other four varieties would be omitted. The same procedure applied to the nonhemolytic varieties would mean that thirty-one strains of this type of streptococci would represent three varieties, namely, *ignavus, fecalis* and nonhemolytic type I and seventeen strains of this type of streptococcus divided among the five other varieties would be omitted. On consulting table 2 it is found that in a few of the sputums that were obtained at the time of a cold in the chest, only those varieties that are to be omitted from the vaccine were present in the sputum.

SUMMARY

In table 1 are presented data for thirty-one patients who were susceptible to chest colds to the extent of having from three to five a year; seventeen were normal persons and fourteen had asthma with their colds but were well between the attacks of asthma. The cases were

under observation for from two to six years; nine were observed for six years, eleven for four years, seven for three years and four for two years.

Some of the patients had more colds in certain months than did others; other patients had more colds in still other months, and others had colds in months that differed from either of the foregoing. Even those patients who were more prone to colds in certain months evidenced considerable variability in different years, so that in general no particular month seemed to have much bearing on the incidence of chest colds, with the exception that during the summer season there were fewer colds.

Since all of these patients lived within a ten mile radius of Boston, extraneous conditions, such as climate, changes in weather, exposures and epidemics, seemed to have little bearing on the incidence of chest colds in general. Exclusive of the summer season, from June to August inclusive, the incidence of chest colds could not be correlated with the presence or absence of sunshine.

In 17 per cent of all instances the interval between colds was one month, in 36.5 per cent two months, in 26 per cent three months, in 9 per cent four months and in 11 per cent five or more months; in other words, nearly two thirds of the patients had colds every two or three months and another one-sixth had colds within a month of the preceding one. Therefore, in general, these patients seemed to have little immunity to chest colds, and a cold produced only a short immunity, if any, against a succeeding cold.

One treatment with a vaccine at the time of a cold for its curative effect, whether it benefited the cold or not, seemed to have no effect on immunity against the succeeding cold. A series of preventive treatments did seem to produce immunity in that the usual number of colds was reduced from three or more to one or even none for one year in most cases.

In table 2 are presented data for fifteen of the former patients in whom a bacteriologic examination of the sputum was made at the time of a chest cold. Streptococci were isolated from practically all of the eighty-two sputums; from only nine sputums was *Staphylococcus pyogenes-aureus* isolated; from one, *Staphylococcus pyogenes-albus;* from two, *Staphylococcus pyogenes-citreus;* from one, *Micrococcus tetragenous* and *sarcinae,* and from twelve, bacilli. Aside from these organisms no others were isolated, and of the bacilli none was among the common pathologic and easily recognized types.

Among the streptococci there was great variability in the types of hemolytic and nonhemolytic and also great variability among the varieties of each type, whether the colds occurred at intervals of one or several months and whether the examinations were made with

several successive sputums in some one year or with one or two sputums a year for several years. Rarely was the same variety present in three successive sputums.

Varieties of streptococci that were more prevalent in one year were less prevalent than some other variety the next year. Therefore, in order to make a mixed streptococcus vaccine to be used either as a curative or as a preventive in chest colds, constant examination of the sputum in chest colds must be made in order to ascertain the more prevalent varieties. The less prevalent varieties occur fairly often, and occasionally they may be the only organisms that are isolated from the sputum at the time of a cold; therefore, in such instances the vaccine consisting of the more prevalent organisms might be ineffective. However, it would seem to be impracticable to incorporate all sixteen varieties of streptococci into a vaccine.

CONCLUSIONS

There is considerable variability in the occurrence of chest colds in those who are very susceptible, and this seems to be an individual characteristic rather than one due to dependence on extraneous conditions.

Bacteriologic examination of the sputum at the time of a chest cold reveals variability among the varieties of streptococcus, which is the organism most constantly isolated.

For these reasons and since a vaccine consisting of the most prevalent varieties of streptococci seems frequently to prevent and often to benefit a cold in the chest, it is fair to assume that streptococci play a part in the cause of colds.

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BLOOD PRESSURE IN SIX THOUSAND PRISONERS AND FOUR HUNDRED PRISON GUARDS

A STATISTICAL ANALYSIS *

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In spite of the large amount of work already done on blood pressure, there is still great need for information in regard to standards of normal. As so often happens in medicine, when physicians first discovered hypertension, they immediately devoted all their efforts to curing it, and only gradually and after many years did they become curious enough to undertake such studies as would enable them to determine when a given pressure represents disease and when it is only a physiologic variation from the average.

Even today there still is great need for a biologic or anthropologic approach to the problem. Figures which are commonly assumed to represent normal or average blood pressure in men and women at various ages are supplied by insurance companies, but these standards are not entirely satisfactory, partly because the original data are so often unreliable, but mainly because the persons measured represent a highly selected group of "accepted risks." It should be obvious that if one decides to accept for insurance only those persons whose blood pressures fall between limits of, let us say, 100 and 140 mm. of mercury, the average is bound to come out about 120 mm. Furthermore, when at the start it was assumed that blood pressure would rise step by step with age, and insurance risks were accepted on that basis, it was foreordained that the means obtained in the different age groups would increase steadily from youth to old age. The fact that enormous numbers of cases are used in the analysis does not improve matters, because the resultant means must still be somewhat artificial. What the insurance companies could do to be more helpful would be to publish percentage distributions and particularly modes representing measurements made on all applicants, accepted and rejected. The mode, which represents the commonest or most typical pressure, will naturally be the measurement of central tendency least affected by errors in sampling or by the inclusion in the group studied of many persons with hypertension.

* Submitted for publication, Nov. 12, 1929.

* From the Division of Medicine, the Mayo Clinic.

What is needed is more information secured from the measurement of men and women chosen at random. But how is this to be done, and where can one find subjects suitable for study? Probably the best standards of blood pressure published so far have come out of those university infirmaries in which the incoming freshmen are put through a physical examination (Lee,[1] Barach and Marks,[2] Alvarez,[3] Diehl and Sutherland,[4] Burlage,[5] Jackson[6]). Unfortunately, most of these students fall between age limits of 18 and 25 years, so the problem remains of finding unselected groups of men and women older than 25.

While puzzling over this difficulty, it occurred to us that it might be well to take advantage of the opportunity that is offered in many places to study the blood pressure of men confined in state prisons. To be sure, these men have been selected, but the criteria were moral, social, financial and political; that is, the prisoners had broken some of the rules of society, they were caught, and they failed in their efforts to escape punishment. The essential point is that there was no selection along physical lines. Fortunately for our purpose, modern anthropologic research has already shown that Lombroso was wrong, and that in their bodily measurements prisoners are no different from their brethren outside the walls (Brasol[7]).

Another possible advantage of studying blood pressure in prisoners may be found in the fact that they have been freed from the hurry and strain and fatigue incident to earning a living. To a certain extent they are under basal conditions (Addis[8]). The disadvantage of this is, of course, that the figures obtained may not be exactly comparable with

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2. Barach, J. H., and Marks, W. L.: Blood Pressures, Their Relation to Each Other and to Physical Efficiency, Arch. Int. Med. **13**:648 (April) 1914.

3. Alvarez, W. C.: Blood Pressure in University Freshmen and Office Patients, Arch. Int. Med. **26**:381 (Oct.) 1920; Blood Pressures in Fifteen Thousand University Freshmen, ibid. **32**:17 (July) 1923.

4. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men Including a Special Study of Those with Hypertension, Arch. Int. Med. **36**:151 (Aug.) 1925.

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6. Jackson, C. M.: The Physique of Male Students at the University of Minnesota: A Study in Constitutional Anatomy and Physiology, Am. J. Anat. **40**:59, 1927; Physical Measurements of the Female Students at the University of Minnesota, with Special Reference to Body Build and Vital Capacity, Am. J. Phys. Anthrop. **12**:363, 1929.

7. Brasol, Boris: Anthropology and Criminology, Am. J. Phys. Anthrop. **12**:339, 1928.

8. Addis, Thomas: Blood Pressure and Pulse Rate Levels, Arch. Int. Med. **29**:539 (April) 1922.

those secured in the world at large; what is wanted is a standard of normal for men as the physician sees them, hard at work.

During the progress of the study here reported, an effort was made to have the men quiet and rested when the pressures were taken. Within a few days after their arrival the prisoners were called to the hospital, usually on Monday mornings or Friday afternoons. After sitting and waiting for an hour they were called in squads of ten or twelve into a room where they undressed to the waist. Their vision was first tested, and then the blood pressure was measured (with the subject standing). If it was found to be high, the measurement was repeated after an hour. Few of the men evinced more than a mild interest in the proceeding. As will be seen later when we come to discuss the measurements on guards, this apathy probably had an influence on the results. The guards were worried for fear something would be found which would interfere with their being employed, and this may account to some extent for the fact that their pressures were higher than those of the prisoners.

The measurements were all made by O'Neil, a well trained hospital orderly who took a keen interest in the work. A mercury manometer was used, and the readings were made in the usual way with a stethoscope.

THE RANGE AND CENTRAL TENDENCIES OF SYSTOLIC BLOOD PRESSURE AT DIFFERENT AGES

Tables 1, 2, 3 and 4, and charts 1 and 2 summarize the measurements made on 5,364 white prisoners. Of these 3,677 were of normal weight, according to O. H. Roger's New York Life standard table; 1,200 were 11 per cent or more overweight and 487 were 11 per cent or more underweight.

Chart 1 shows graphically how the blood pressure varies with age. The striking feature of these percentage distributions is that the mode or peak remains on the same abscissal line in all the polygons. In other words, in this group of prisoners, a few begin to show hypertension during early and middle life, but most of them reach middle life or old age with pressures no greater than those which they probably had in youth. In the group aged from 40 to 45 years, there begin to appear a number of persons with pressures of 140 mm. or more, but this increase in the incidence of hypertension is not marked until after the age of 50. The failure of the modal or most typical pressure to increase in the first five decades of life is shown also in chart 2. There we have plotted the calculated modes which correspond closely to those which can be located by inspection of the distributions.

We again emphasize the fact that it is this mode which should be of the greatest interest to clinicians when, as so often happens, they wish

TABLE 1.—*Systolic Blood Pressure of White Prisoners with Weight Within 10 Per Cent of Normal Average (Mexicans Are Excluded, Syphilitic Prisoners Are Included)*

Pressure in Millimeters	Age, Years																						Total	Per Cent	Cumulated Percentage	Pressure in Millimeters
	15-18	19	20	21	22	23	24	25	26	27	28	29	30-31	32-33	34-35	36-37	38-39	40-44	45-49	50-59	60-84					
80-89	..	..	3	1	2	..	..	1	..	..	1	..	..	1	3	2	..	2	1	..	..	17	0.46	0.46	80-89
90-99	7	20	12	13	17	8	17	6	11	5	2	6	14	14	5	11	7	12	7	11	..	205	5.58	6.04	90-99
100-109	24	51	43	60	74	62	59	43	49	36	36	30	48	42	36	24	33	33	22	15	5	825	22.45	28.49	100-109
110-119	36	56	62	75	87	83	63	58	53	66	48	41	59	63	65	39	36	53	45	31	13	1132	30.75	59.24	110-119
120-129	28	34	53	55	75	54	64	46	41	44	43	19	50	66	38	27	24	47	29	23	11	871	23.69	82.93	120-129
130-139	11	26	27	22	30	16	22	27	13	19	12	9	24	24	15	12	15	28	15	20	8	395	10.76	93.69	130-139
140-149	4	2	10	8	7	8	7	1	6	8	3	5	6	7	7	8	3	14	13	17	6	150	4.08	97.77	140-149
150-159	1	1	1	2	2	2	4	1	..	4	3	..	3	1	2	..	1	4	4	10	8	54	1.47	99.24	150-159
160-169	..	..	..	..	3	2	..	2	..	1	..	1	1	..	1	..	1	..	..	4	2	18	0.49	99.73	160-169
170-179	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	..	3	5	0.14	99.87	170-179
180-189	..	..	1	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	2	2	0.05	99.92	180-189
190-199	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	2	0.05	99.97	190-199
200-209	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	....	.....	.....	200-209
210-219	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	....	.....	.....	210-219
220-229	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	0.03	100.00	220-229
Total	111	190	212	236	297	235	237	185	173	183	148	111	205	218	172	123	120	194	137	132	58	3677			
Mean	117.5	115.3	118.4	116.8	117.2	117.1	117.5	118.2	115.8	119.4	118.0	116.4	117.8	118.0	117.8	116.9	117.1	120.4	120.9	126.0	135.5	118.3			
Standard deviation	12.3	12.6	13.9	12.4	13.1	12.3	13.6	12.4	11.5	12.8	11.8	12.6	13.3	12.3	12.9	13.6	13.1	14.9	15.2	19.1	23.8	13.8			
Probable error of the mean	0.8	0.6	0.6	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.8	0.6	0.6	0.7	0.8	0.8	0.7	0.9	1.1	2.1	0.2			
Median	116.9	114.3	117.7	115.9	116.4	115.8	116.8	117.3	115.0	117.6	117.3	114.7	116.9	118.3	116.5	116.3	115.6	119.4	118.6	123.9	130.0	117.0			
Mode	115.7	112.0	116.3	114.1	114.8	113.2	115.0	115.5	113.7	113.4	115.9	111.3	115.1	118.9	113.9	115.4	112.6	117.4	114.3	119.7	119.0	114.4			
Coefficient of variation	10.5	10.9	11.7	10.5	11.2	10.5	11.6	10.5	9.9	10.7	10.0	10.8	11.3	10.4	11.0	11.7	11.2	12.3	12.6	15.1	17.6	11.7			
Percentage above 140 mm	4.5	1.6	5.7	4.2	4.0	5.1	5.1	2.2	3.5	7.1	4.1	5.4	4.9	3.7	5.8	6.5	4.2	9.8	13.1	24.3	36.2	6.3			

TABLE 2.—*Systolic Blood Pressure of White Prisoners with Weight 11 Per Cent or More Above Normal (Mexicans Are Excluded, Syphilitic Prisoners Are Included)*

Pressure in Millimeters	Age, Years																					Total	Per Cent	Cumulated Per-centage	Pressure in Millimeters
	15-18	19	20	21	22	23	24	25	26	27	28	29	30-31	32-33	34-35	36-37	38-39	40-44	45-49	50-59	60-84				
80-89	..	..	..	1	..	..	..	..	..	1	1	..	..	..	1	..	..	..	1	..	..	5	0.42	0.42	80-89
90-99	5	6	4	4	9	..	3	2	6	2	2	2	1	..	3	1	1	3	2	3	..	59	4.92	5.34	90-99
100-109	21	13	30	21	26	18	17	15	9	12	13	4	6	10	7	9	3	10	4	3	2	253	21.11	26.45	100-109
110-119	17	33	18	28	29	29	23	19	22	22	6	10	20	14	8	10	10	15	7	5	1	346	28.82	55.27	110-119
120-129	11	19	24	24	25	20	17	21	7	11	11	11	14	11	5	6	12	9	5	6	1	270	22.50	77.77	120-129
130-139	5	12	7	6	16	15	3	11	5	10	7	4	7	8	6	3	6	13	7	5	3	159	13.25	91.02	130-139
140-149	2	2	3	7	4	6	2	1	2	7	3	2	3	7	..	..	3	7	6	8	1	76	6.33	97.35	140-149
150-159	..	1	1	2	..	..	1	..	4	..	..	..	1	1	..	..	1	..	2	4	1	19	1.58	98.93	150-159
160-169	..	2	1	..	1	..	..	..	..	..	..	..	..	2	..	..	..	1	1	1	1	10	0.83	99.76	160-169
170-179	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	1	0.08	99.84	170-179
180-189	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	180-189
190-199	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	1	0.08	99.92	190-199
200-209	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	200-209
210-219	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	210-219
220-229	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	220-229
230-239	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	230-239
240-249	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	240-249
250-259	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	250-259
260-269	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	260-269
270-279	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	0.08	100.00	270-279
Total	61	88	88	93	110	88	66	69	55	65	43	33	52	53	30	29	36	59	35	36	11	1200	100.00		
Mean	114.3	119.3	117.0	118.6	117.7	120.7	116.5	118.9	118.3	120.1	118.3	120.2	121.3	124.8	115.3	115.3	123.9	123.6	126.1	131.7	*145.0	119.9			
Median	112.9	117.6	115.6	117.5	116.9	119.0	115.7	119.5	115.9	118.2	120.0	120.9	119.5	122.7	115.0	115.0	123.3	122.2	128.0	132.0	133.3	118.2			
Mode	110.1	114.2	112.8	115.3	115.3	115.6	114.1	120.7	111.1	114.4	123.4	122.3	115.9	118.5	114.4	114.4	122.1	119.4	131.8	132.6	109.9	114.8			

* If the 270 reading is omitted the mean is 132.0 mm.

TABLE 3.—*Systolic Blood Pressure of White Prisoners with Weight 11 Per Cent or More Under Normal (Mexicans are Excluded, Syphilitic Prisoners are Included)*

Pressure in Millimeters	Age, Years					Total	Per Cent	Cumulative Percentage
	15-24	25-29	30-39	40-49	50-84			
80-89	..	3	1	2	3	9	1.85	1.85
90-99	9	8	21	17	3	58	11.91	13.76
100-109	22	13	51	24	5	115	23.61	37.37
110-119	14	17	38	29	20	118	24.24	61.61
120-129	13	16	26	22	17	94	19.29	80.90
130-139	3	9	15	10	12	49	10.06	90.96
140-149	2	1	5	7	11	26	5.34	96.30
150-159	..	2	1	4	3	10	2.05	98.35
160-169	..	..	1	2	3	6	1.23	99.58
170-179	..	1	..	..	..	1	0.21	99.79
180-189	..	..	..	..	..	...	.....	.....
190-199	..	..	..	..	..	...	.....	.....
200-209	..	..	..	..	1	1	0.21	100.00
Total	63	70	159	117	78	487		
Mean	112.6	116.9	114.0	117.1	126.5	116.8		
Median	110.7	116.5	111.8	115.5	124.7	115.2		
Mode	106.9	115.7	107.4	112.3	121.1	112.1		

TABLE 4.—*Systolic Blood Pressure of White Prisoners, All Weights*

Pressure in Millimeters	Age, Years						Total
	15-24	25-29	30-39	40-49	50-84	40-84	
80-89	7	7	8	6	3	9	31
90-99	134	52	78	41	17	58	322
100-109	541	260	269	93	30	123	1,193
110-119	653	362	362	149	70	219	1,596
120-129	516	270	279	112	58	170	1,235
130-139	221	126	135	73	48	121	603
140-149	74	39	49	47	43	90	252
150-159	18	14	11	14	26	40	83
160-169	9	4	6	4	11	15	34
170-179	...	1	...	3	3	6	7
180-189	2	...	...	...	...	...	2
190-199	...	...	...	...	3	3	3
200-209	...	...	...	...	1	1	1
210-219	...	...	...	...	...	...	.....
220-239	...	...	...	...	1	1	1
240-249	...	...	...	...	...	...	.....
250-259	...	...	...	...	...	...	.....
260-269	...	...	...	...	...	...	.....
270-279	...	...	...	...	1	1	1
Total	2,175	1,135	1,197	542	315	857	5,364
Mean	117.2	118.0	117.7	120.5	129.2	123.7	118.5
Standard deviation	13.1	13.0	13.4	16.1	22.4	19.1	14.5
Probable error of the mean	0.2	0.3	0.3	0.5	0.8	0.4	0.1
Median	117.2	116.9	116.7	118.8	126.4	121.1	117.1
Mode	114.2	114.7	114.7	115.4	120.8	115.9	114.3
Coefficient of variation	11.2	11.0	11.4	13.4	17.3	15.4	12.2
Percentage above 140 mm	4.7	5.2	5.5	12.6	28.2	18.3	7.2

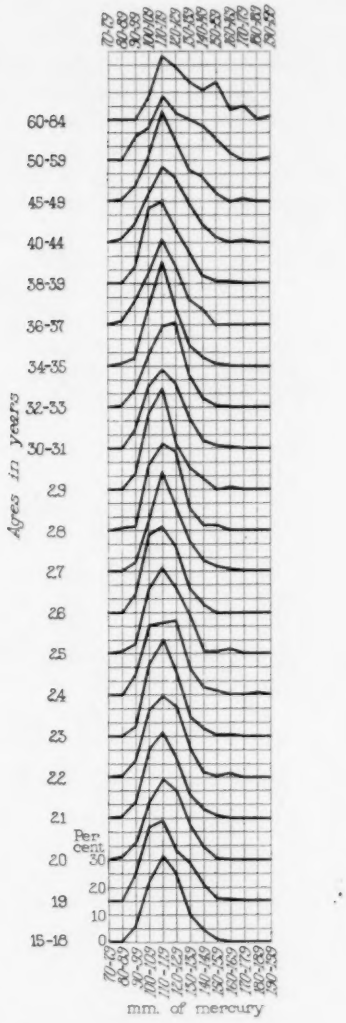

Chart 1.—Percentage distribution polygons showing systolic blood pressure in white prisoners of normal weight and different ages. The ordinates represent percentages; the abscissas represent blood pressure in millimeters of mercury.

to know what normal blood pressure should be for a given patient. The mean or arithmetic average which has been used so commonly in the past is not a reliable index of normal, because it is so markedly affected by the measurements made on persons who are abnormal. In the prisoners studied by us there was so little hypertension, especially among the younger men, that the polygons were fairly symmetrical, and the means year by year were not much larger than the modes. For prisoners of normal weight and middle age the means ranged closely

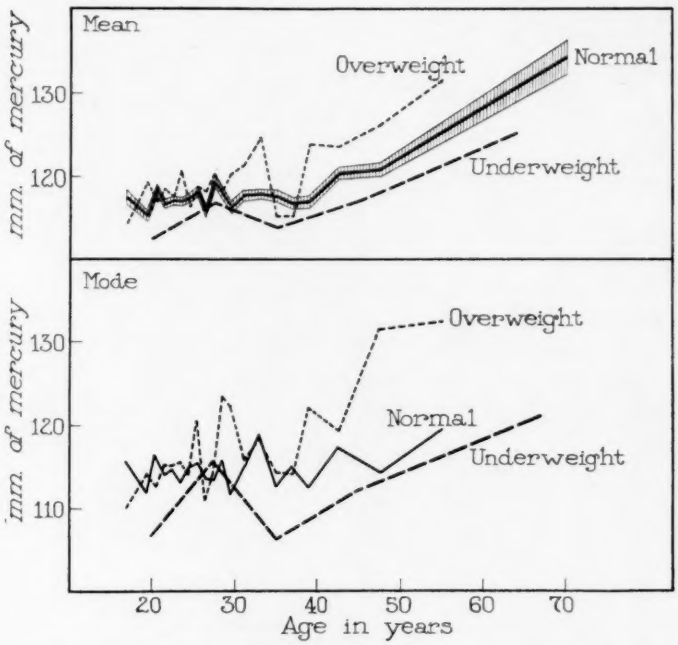

Chart 2.—Mean and modal systolic blood pressures year by year in 5,364 white prisoners. The shaded area on each side of the line which represents the mean shows the range of the probable error of the mean. The lines above and below those representing the means and modes represent mean and modal pressures of prisoners who are 11 per cent or more overweight or 11 per cent or more underweight. The ordinates represent pressures in millimeters of mercury; the abscissas represent ages.

about 117 mm. of mercury. Most of the statisticians who have worked with measurements made during examinations for insurance agree that the means should be about 125 mm.

In chart 1 it can be seen that if the percentage distribution polygons were symmetrical, 140 mm. would represent the upper limit of normal

pressure, and this agrees well with the experience of clinicians and insurance examiners. The lower limit of normal appears to be 90 mm. Taking 140 mm. as the dividing line between normal and pathologic, it appears that 5 per cent of the white prisoners of all weights and ages between 15 and 39 years had hypertension. As will be seen in tables 1 and 4, this percentage was fairly constant in the various age groups, and there were few accessions to the ranks of those with hypertension until after the age of 40 years.

There were few prisoners with pressures higher than 180 mm. At first when we began to study the figures, it seemed to us that there were too few cases of hypertension, and that possibly the examiner might have had a tendency to read low, but later when we came to study the measurements made on prison guards, we saw that this explanation could hardly be correct.

Some readers may be surprised to find that modal blood pressure does not show any tendency to rise until after the age of 45, but as Stocks and Karn [9] have noted in a recent review of the subject, this absence of a linear correlation between age and blood pressure seems now to be definitely established, and even the averages published by insurance companies demonstrate it (Symonds [10]). Still more surprising is the observation recently made by several students of the subject that the mean and modal pressures tend actually to decrease during the third decade of life (Alvarez,[3] Burlage [5]). This tendency is shown in chart 6, which represents mean and modal pressure year by year in guards.

The figures of Diehl and Sutherland, when compared with those of Alvarez, show that the younger college entrants are so sensitive and reactive that they respond to excitement with an elevation of blood pressure. With increasing age, they appear to become more phlegmatic, so that after the age of 30 their modal pressure (at the University of California) is almost as low as that of the prisoners.

The fact that in chart 2 the curve representing yearly mean blood pressure begins to rise before that representing modal pressure again brings out the fact that oncoming age causes hypertension to appear in an occasional subject long before it produces a small increase in the pressure of almost everyone in the group. As has already been pointed out, there is a fairly large number of persons in whom hypertension does not develop, no matter how long they live. Of the fifty-eight prisoners aged from 60 to 84 years, and of normal weight, thirty-seven, or 64 per cent, had pressures less than 139 mm. of mercury. Our impression,

9. Stocks, Percy, and Karn, M. N.: Blood Pressure in Early Life. A Statistical Study, Cambridge, University Press, 1924, p. 1.

10. Symonds, Brandreth: The Blood Pressure of Healthy Men and Women, J. A. M. A. **80**:232 (Jan. 27) 1923.

therefore, is that a pressure of 115 mm. is just as normal and a pressure of 140 mm. just as abnormal in an old man as in a young one.

Chart 2 confirms what is already known (Symonds, Alvarez and Zimmermann,[11] Alvarez, McCalla and Zimmermann,[12] and Huber[13]), and that is that fatness and leanness have a definite influence on blood

TABLE 5.—*Systolic Blood Pressure in Negro Prisoners, All Weights*

All Weights					
	Age, Years				
Pressure in Millimeters	16-24	25-29	30-39	40-84	Total
90-99	5	2	1	..	8
100-109	15	6	8	3	32
110-119	25	7	5	2	39
120-129	18	7	7	1	33
130-139	9	8	6	2	25
140-149	5	..	4	2	11
150-159	3	..	..	..	3
160-169	1	..	1	1	3
170-179	..	..	..	1	1
Total	81	30	32	12	155
Mean	120.3	119.3	123.1	125.8	121.5
Standard deviation	15.1	12.6	16.1	22.5	15.8
Probable error of the mean	1.1	1.6	1.9	6.5	0.9
Median	118.2	120.0	122.9	130.0	119.6
Mode	113.7	121.4	122.5	138.4	115.8
Percentage above 140 mm.	11.1	0.0	15.7	33.3	11.6

Normal Weight					
	Age, Years				
Pressure in Millimeters	16-24	25-29	30-39	40-84	Total
90-99	3	2	1	..	6
100-109	11	3	6	2	22
110-119	12	3	3	2	20
120-129	8	5	7	1	21
130-139	6	5	3	2	16
140-149	1	..	2	1	4
150-159	2	..	..	..	2
160-169	1	..	1	1	3
170-179	..	..	..	1	1
Total	44	18	23	10	95
Mean	119.3	119.4	122.0	132.0	121.3
Standard deviation	14.4	13.4	16.3	22.8	16.9
Probable error of the mean	1.4	2.1	2.3	4.9	1.2
Median	116.7	122.0	122.1	130.0	119.8
Mode	111.4	127.1	122.5	126.0	116.7
Percentage above 140 mm.	3.1	0.0	13.0	30.0	10.5

11. Alvarez, W. C., and Zimmermann, Arnold: Blood Pressure in Women as Influenced by the Sexual Organs, Arch. Int. Med. **37**:597 (May) 1926.

12. Alvarez, W. C.; McCalla, R. L., and Zimmermann, Arnold: Hypertension and Constipation, Arch. Int. Med. **38**:158 (Aug.) 1926.

13. Huber, E. G.: Systolic Blood Pressures of Healthy Adults in Relation to Body Weight, J. A. M. A. **88**:1554 (May 14) 1927.

pressure. It is not so generally known that leanness and stoutness have little effect on blood pressure until after the age of 37. Alvarez and Zimmermann, who studied 1,182 women (see chart 2 in their article),

TABLE 6.—*Systolic Blood Pressure of Mexican Prisoners, All Weights*

Pressure in Millimeters	All Weights: Age, Years 15-24	25-29	30-39	40-68	Total	Per Cent
80–89	1	1	..	..	2	0.3
90–99	25	10	9	4	48	7.2
100–109	67	35	32	9	143	21.6
110–119	113	39	41	20	213	31.9
120–129	70	40	27	9	146	21.9
130–139	32	19	9	8	68	10.2
140–149	17	7	5	4	33	4.9
150–159	3	3	..	2	8	1.2
160–169	...	..	1	1	2	0.3
170–179	...	..	..	..	...	....
180–189	3	..	..	..	3	0.5
Total	331	154	124	57	666	100.0
Mean	118.0	118.4	116.2	120.8	118.0	
Standard deviation	14.5	14.2	12.7	15.7	14.2	
Probable error of the mean	0.5	0.8	0.8	1.4	0.4	
Median	116.4	118.0	115.2	117.8	116.6	
Mode	113.2	117.2	112.9	111.8	113.8	
Percentage above 140 mm	6.9	6.5	4.8	12.3	6.9	

Pressure in Millimeters	Normal Weight: Age, Years 15-24	25-29	30-39	40-68	Total	Per Cent
80–89	1	..	..	..	1	0.2
90–99	17	6	5	3	31	6.4
100–109	45	30	25	6	106	21.8
110–119	88	32	30	12	162	33.3
120–129	50	26	25	6	107	21.9
130–139	25	9	7	4	45	9.2
140–149	12	5	5	4	26	5.3
150–159	2	3	..	..	5	1.0
160–169	...	..	1	..	1	0.2
170–179	...	..	..	..	...	....
180–189	3	..	..	..	3	0.6
Total	243	111	98	35	487	99.9
Mean	118.4	117.6	117.5	119.0	118.1	
Standard deviation	14.8	13.5	12.9	14.2	14.1	
Probable error of the mean	0.6	0.9	0.9	1.6	0.4	
Median	116.6	116.1	116.3	117.1	116.5	
Mode	112.7	113.1	113.9	113.3	113.3	
Percentage above 140 mm	7.0	7.2	6.1	11.4	7.1	

found that in them fatness began to cause an increase in pressure during the third decade of life while leanness did not lower it much until the fourth decade. When one compares the summaries given in tables 1, 2 and 3, it will be seen that the modal pressure for white prisoners of normal weight was 114.4 mm., that for overweight prisoners was 114.8

mm. and that for underweight prisoners was 112.1. The corresponding means in the three groups were 118.3, 119.9 and 116.8 mm., respectively. These differences are less striking than those that have been found in office patients and in persons examined for insurance.

Racial Differences in Blood Pressure.—Tables 5 and 6, and chart 3 show the distribution and central tendencies of blood pressure in negroes and Mexicans. Unfortunately the groups are a little too small for safe conclusions, but they show that blood pressure in Mexicans does not rise with age, while that in negroes rises more rapidly than in white Americans. The effects of overweight and underweight in the negro and Mexican seem to be about the same as in the white American.

There were forty Chinese of all ages. Twenty-two were normal in weight, and fourteen were underweight. Their modal pressure was 113.6 mm., and their mean pressure was 125.3 ± 1.9 mm.

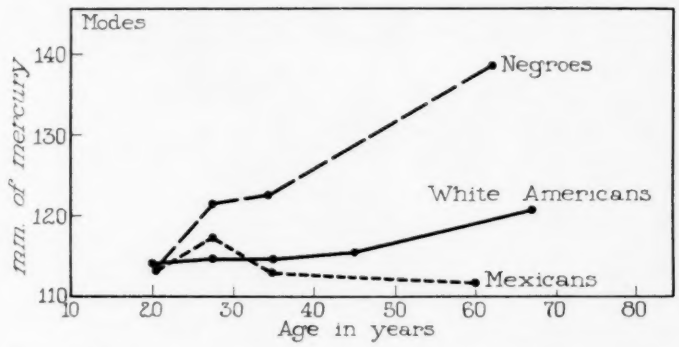

Chart 3.—Modal systolic blood pressure for white American prisoners, for negroes and for Mexicans, of all weights.

Effect of Syphilis.—As pointed out in a recent article (Stanley [14]), 9.2 per cent of the prisoners showed a positive Wassermann reaction of the blood. Table 7 and chart 4 suggest that during the first four decades of life syphilis has no effect on systolic blood pressure. After the age of 40 it appears to be beneficial in so far as it helps to maintain a youthful level of pressure.

Effects of the Previous Use of Alcohol and Drugs.—Twenty-one per cent of all the prisoners admitted having used alcohol more or less habitually before their incarceration. Most of them had, for some time before the examination, been deprived of liquor on account of their

14. Stanley, L. L.: Syphilis Among State Prisoners, J. A. M. A. **92**:1238 (April 13) 1929.

TABLE 7.—*Systolic Blood Pressure of Syphilitic Prisoners, Normal Weight*

Pressure in Millimeters	Age, Years				Total
	16-24	25-29	30-39	40-84	
80-89	..	..	1	2	3
90-99	8	10	6	5	29
100-109	33	21	24	18	96
110-119	44	30	35	21	130
120-129	25	18	22	14	79
130-139	12	11	14	4	41
140-149	7	2	2	11	22
150-159	1	..	..	5	6
160-169	..	2	1	1	4
Total	130	94	105	81	410
Mean	116.9	116.8	117.1	120.7	117.6
Standard deviation	12.8	13.5	12.9	18.1	14.4
Probable error of the mean	0.8	0.9	0.9	1.4	0.5
Median	115.5	115.3	116.1	117.4	115.9
Mode	112.5	112.7	114.3	110.8	112.5
Percentage above 140 mm	6.2	4.3	2.9	21.0	7.8

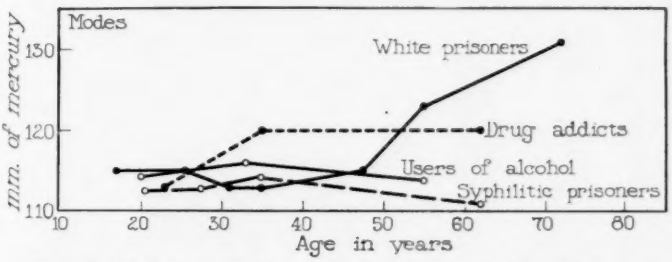

Chart 4.—Modal systolic blood pressure in white healthy prisoners, in drug addicts, in users of alcohol and in prisoners with positive Wassermann reactions, all weighing within 10 per cent of the normal average.

TABLE 8.—*Systolic Blood Pressure of Users of Alcohol, Normal Weight*

Pressure in Millimeters	Age, Years			Total
	15-25	26-39	40-70	
80-90	1	3	..	4
90-99	20	7	4	31
100-109	87	17	30	134
110-119	112	20	58	190
120-129	79	16	39	134
130-139	40	15	24	79
140-149	15	5	16	36
150-159	3	2	10	15
160-169	...	1	2	3
Total	357	86	183	626
Mean	117.4	119.0	123.0	119.2
Standard deviation	12.7	16.6	14.9	14.2
Probable error of the mean	0.5	1.2	0.7	0.4
Median	116.3	118.0	119.9	117.6
Mode	114.1	116.1	113.7	114.4
Percentage above 140 mm	5.0	9.3	15.3	8.6

imprisonment in county jails. The pressures of the 626 who were of normal weight are analyzed in table 8 and chart 4.

All lovers of the cup that cheers will be rejoiced and perhaps encouraged to learn that the mean blood pressure of the users of alcohol was no different from that of the abstainers. Moreover, chart 4 shows that the calculated mode did not tend to rise with age as much as it usually does. Naturally, in order to merit general acceptance, these observations will have to be confirmed on other groups of men, and particularly on groups in which care has been taken to establish for each user of alcohol the amount of the drug consumed, the way in which it was consumed (day by day or in occasional debauches) and the length

TABLE 9.—*Systolic Blood Pressure of Drug Addicts, Normal Weight*

Pressure in Millimeters	Age, Years			Total
	16-29	30-39	40-84	
80-89	1	..	..	1
90-99	1	3	1	5
100-109	18	8	3	29
110-119	30	13	8	51
120-129	17	15	8	40
130-139	8	4	4	16
140-149	3	3	4	10
150-159	1	..	2	3
160-169	1	..	1	2
Total	80	46	31	157
Mean	118.5	118.9	126.6	120.2
Standard deviation	13.1	12.4	16.3	14.0
Probable error of the mean	1.0	1.2	2.0	0.8
Median	116.7	119.2	124.4	118.5
Mode	113.0	119.9	119.9	115.2
Percentage above 140 mm.	6.3	6.5	22.6	9.6

of interval elapsed between the period of the habitual drinking and the taking of the blood pressure. The fact, however, that in this group of prisoners there was no significant difference between the pressures of abstainers and drinkers makes it seem improbable that any will be found in the future.

Two hundred and eighty-four (4.6 per cent) of the 6,225 prisoners admitted having used drugs, but at the time of examination all were, perforce, more or less over the habit. Table 9 and chart 4 suggest that in drug addicts there is a slight increase above normal in the modal pressure during the fourth and fifth decades of life.

Effect of Tobacco.—Six and four-tenths per cent, or 288, of the 4,507 men aged between 15 and 39 years did not use tobacco. In the group aged from 25 to 39 years the percentages of underweight, normal and overweight men were practically the same as in the group of

smokers, but in the group aged from 15 to 24 years the percentage of overweight men was significantly greater than in the corresponding group of smokers.

The mean blood pressure for the nonsmokers was 116.4 ± 0.5 mm. This is 1.2 ± 0.5 mm. less than the mean for 3,931 smokers. As the difference is only twice its probable error, it is hardly significant. Much more significant is the fact that the calculated mode for nonsmokers is low: 110.7 mm. as compared with 114.7 mm. for 4,507 smokers and nonsmokers taken together. The percentage with pressures higher than 140 mm. was 5.9, which is practically the same as that of the 4,507.

TABLE 10.—*Diastolic Blood Pressure of White Prisoners, Normal Weight*

	Age, Years				
Pressure in Millimeters	15-24	25-29	30-39	40-84	Total
20-29	3	...	...	1	4
30-39	7	2	...	...	9
40-49	40	14	9	6	69
50-59	174	73	53	25	325
60-69	339	138	151	82	710
70-79	348	201	212	107	868
80-89	128	79	78	70	355
90-99	35	22	31	39	127
100-109	3	1	2	6	12
110-119	...	1	...	3	4
120-129	...	...	...	...	...
130-139	...	...	...	1	1
Total	1,077	531	536	340	2,484
Mean	69.0	71.2	72.4	75.9	71.2
Standard deviation	11.8	11.5	10.8	13.5	12.0
Probable error of the mean	0.2	0.3	0.3	0.5	0.2
Median	69.3	71.9	72.6	75.2	71.4
Mode	68.3	68.9	72.9	74.0	70.3

These observations suggest that tobacco raises slightly the pressure of most of its users, but does not produce pathologic hypertension.

To a considerable extent this study confirms that of Johnson,[15] who found no difference in the mean blood pressure of two small groups of smokers and nonsmokers.

The Effect of Warm and Cool Weather.—The mean of the blood pressure readings made on seventy-four prisoners on warm days was 117.8 mm. ± 1 mm. The mean of another group of 135 men of similar ages, measured on cool days, was 122.7 ± 0.8 mm. It would seem obvious from this and other observations made during the past by Oliver [16] and others that if blood pressure readings are to be comparable,

15. Johnson, W. M.: Tobacco Smoking. A Clinical Study, J. A. M. A. **93**: 665 (Aug. 31) 1929.

16. Oliver, George: Studies in Blood Pressure, Physiological and Clinical, ed. 3, London, H. K. Lewis & Company, 1916, pp. 240.

they should always be accompanied by a record of the temperature of the air at the time. It may well be that differences in temperature account for some or all of the differences in mean blood pressure reported by different observers in different places. They may account also for the marked differences in mean pressure observed from year to year in the same place (Alvarez,[17] Diehl and Sutherland, Symonds).

Influence of Type of Crime.—Having in mind the marked influence that excitement and emotion and perhaps temperament have on blood pressure, we were curious to determine whether the readings on murderers would be any different from those made on the other prisoners. There were eighty-one men between the ages of 15 and 39 who had been convicted of first degree murder, and their mean blood pressure was 120.8 ± 1.2 mm. The difference (+ 3 ± 1.2 mm.) between this and the mean for all prisoners of like ages is probably significant. A greater incidence of hypertension in murderers is shown also by the fact that whereas in the whole group of prisoners there were only 7.2 ± 0.2 per cent with pressures over 140 mm., in this special group there were 12.3 ± 2.8 per cent with such pressures.

It is curious that a similar increase in mean blood pressure was not demonstrable either in second degree murderers or in the men who committed assault with a deadly weapon or with intent to kill. This suggests that the mental make-up that permits or causes a man to attempt the killing of his fellows has no permanent effect on the pressure regulating mechanism, and that the slight hypertension observed in many of the first degree, efficient and successful murderers was produced by worry over their trial and punishment.

DIASTOLIC PRESSURE AND PULSE PRESSURE

Chart 5 and table 1 show that the rise in the line representing modal diastolic pressure comes some time before that in the line representing systolic pressure. As a result modal pulse pressure decreases slightly during the years between the ages of 27 and 47. This has been observed by others, and it may help to explain some of the loss of circulatory efficiency that begins to appear during middle life.

The modal diastolic pressure in prisoners aged from 15 to 29 years was about 68 mm.; in those aged from 30 to 84 years it was about 73 mm. Modal pulse pressure decreased gradually from 46.5 mm. at the age of 20 years to 42 mm. at the age of 40 years.

Fatness and leanness each had a slight effect on the diastolic pressure. The mean diastolic pressure of Mexicans, young negroes, users of drugs and prisoners with syphilis appeared to be normal, but the mean for the

17. Alvarez (footnote 3, second reference).

older negroes, aged over 40 years, was 6.6 ± 3 mm. higher than the mean for white Americans of the same age. As one might expect from the prevalence of lesions of the aortic valve in syphilitic persons, the pulse pressure of the older prisoners with a positive Wassermann reaction was a little larger than that of healthy men.

CORRELATIONS BETWEEN BLOOD PRESSURE AND VARIOUS BODY MEASUREMENTS AND BUILDS

It has already been shown in chart 2 that there is a relationship between body weight and systolic blood pressure, particularly during the later years of life. This relationship has been analyzed more minutely in

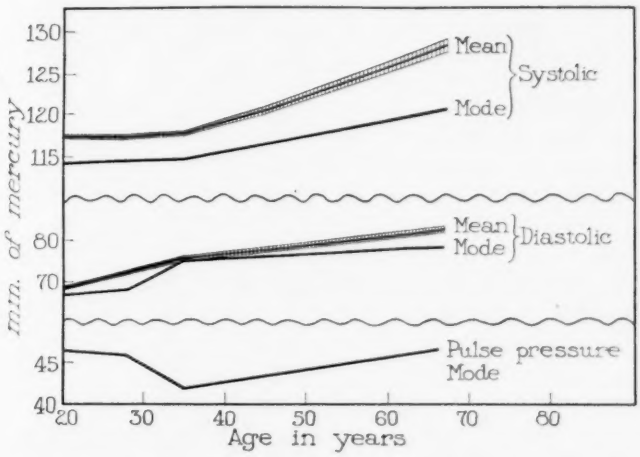

Chart 5.—Mean and modal systolic and diastolic blood pressures in all white prisoners of all weights. The lowest line represents modal pulse pressure. The ordinates represent pressures, and the abscissas represent yearly age groups.

table 11. There it is shown that the coefficient increases from + 0.100 ± 0.013 about the age of 20 years to + 0.205 ± 0.022 about the age of 35 years, and then decreases to + 0.117 ± 0.038 about the age of 60 years.

We have the impression from working with office patients that in them fatness and leanness have more effect on the level of blood pressure than they have in the prisoners, but in the absence of a careful statistical analysis we cannot be positive. The matter is of considerable importance when one is faced with the problem of appraising the significance of a small difference in the mean blood pressure of two groups of men or women. As was shown by Alvarez and Zimmermann, such a differ-

TABLE 11.—*Correlation Tables Showing Relation Between Weight and Systolic Blood Pressure at Different Ages*

Weight in Kilograms	Systolic Blood Pressure in Millimeters of Mercury												
	80-89	90-99	100-109	110-119	120-129	130-139	140-149	150-159	160-169	170-179	180-189	190-199	200+	Total
Ages, 15-24 Years *														
98+	..	...	...	1	...	1	1	..	..	..	..	..	..	3
94-97	..	...	...	1	1	...	..	..	..	..	..	..	..	2
90-93	..	...	2	1	2	...	1	..	1	..	..	..	..	7
86-89	..	...	8	6	5	3	3	..	..	..	..	..	..	25
82-85	..	3	19	34	16	10	7	1	..	..	..	..	..	90
78-81	..	6	24	41	40	20	3	1	..	..	..	..	..	135
74-77	..	15	59	63	68	25	9	2	2	..	..	..	..	243
70-73	1	22	93	115	95	40	14	5	2	..	..	..	..	387
66-69	2	33	128	142	109	52	14	3	3	..	2	..	..	488
62-65	2	17	91	119	89	33	10	2	..	..	..	..	..	363
58-61	1	20	80	85	57	23	6	1	..	..	..	..	..	273
54-57	1	9	31	26	22	13	2	2	..	..	..	..	..	106
50-53	1	8	8	13	8	1	4	1	..	..	..	..	..	44
46-49	..	...	2	1	...	...	..	..	..	..	..	..	..	3
Total	8	133	545	648	512	221	74	18	8	..	2	..	..	2,169
Ages, 25-29 Years †														
98+	..	...	...	2	3	1	1	1	..	..	..	..	..	8
94-97	..	...	1	...	2	2	1	..	..	..	..	..	..	6
90-93	..	...	3	2	3	1	1	..	..	..	..	..	..	10
86-89	..	...	4	7	6	4	2	1	..	..	..	..	..	24
82-85	..	3	10	16	12	3	4	1	..	..	..	..	..	49
78-81	1	5	20	29	12	10	3	1	..	..	..	..	..	81
74-77	..	3	20	36	28	25	5	1	..	..	..	..	..	118
70-73	1	9	55	72	47	25	7	1	1	..	..	..	..	218
66-69	1	8	54	77	54	27	10	1	2	1	..	..	..	235
62-65	..	11	50	63	53	4	3	2	1	..	..	..	..	187
58-61	1	7	29	33	30	15	1	2	..	..	..	..	..	118
54-57	1	5	13	19	15	9	2	3	..	..	..	..	..	67
50-53	1	...	2	2	2	...	..	..	..	..	..	..	..	7
46-49	..	...	2	1	1	...	..	..	..	..	..	..	..	4
Total	6	51	263	359	268	126	40	14	4	1	..	..	..	1,132
Ages, 30-39 Years ‡														
98+	..	...	1	3	2	2	3	..	2	..	..	..	..	13
94-97	..	...	2	2	4	...	..	..	..	..	..	..	..	8
90-93	1	1	3	1	2	3	1	..	..	..	..	..	..	12
86-89	..	...	8	9	4	3	..	1	..	..	..	..	..	25
82-85	..	3	8	15	13	7	2	1	..	..	..	..	..	49
78-81	..	4	7	17	19	12	5	1	..	..	..	..	..	65
74-77	..	2	17	33	20	11	5	..	..	..	..	..	..	88
70-73	..	7	33	43	48	20	6	1	2	..	..	..	..	160
66-69	1	12	42	69	47	16	8	1	..	..	..	..	..	196
62-65	5	9	40	43	25	14	3	1	..	..	..	..	..	140
58-61	1	8	23	24	22	4	3	1	..	..	..	..	..	86
54-57	..	4	16	13	4	3	..	..	..	..	..	..	..	40
50-53	..	4	4	1	..	5	1	..	..	..	..	..	..	15
46-49	..	3	3	...	...	...	..	..	..	..	..	..	..	6
Total	8	57	207	273	210	100	37	7	4	..	..	..	..	903
Ages, 40-49 Years #														
98+	..	...	1	1	3	2	1	1	..	..	..	..	..	9
94-97	..	1	...	4	...	1	..	..	..	..	..	..	..	6
90-93	..	...	1	2	...	2	..	..	..	..	..	..	..	5
86-89	..	1	1	1	4	3	2	..	..	..	..	..	..	12
82-85	..	...	3	3	2	2	..	..	..	1	..	..	..	11
78-81	..	1	7	7	9	3	2	..	1	..	..	..	..	32
74-77	..	1	6	11	7	7	4	1	..	..	..	..	..	37
70-73	..	...	8	17	14	5	5	1	1	..	..	..	..	51
66-69	..	5	15	13	13	9	7	..	..	..	..	..	..	62
62-65	..	8	5	14	10	7	3	..	..	..	..	..	..	47
58-61	..	5	9	6	5	3	..	1	..	..	..	..	..	29
54-57	..	...	2	3	1	1	..	1	1	..	..	..	..	9
50-53	..	1	1	1	...	1	..	..	..	..	..	..	..	4
46-49	..	2	1	...	...	...	..	..	..	..	..	..	..	3
Total	..	25	60	83	68	46	24	7	2	2	..	..	..	317
Ages, 50-84 Years §														
98+	..	...	...	1	...	1	..	1	1	..	..	..	1	5
94-97	..	...	2	...	...	2	..	..	..	..	..	..	..	4
90-93	..	...	1	1	2	1	1	..	..	..	..	..	..	7
86-89	..	...	...	1	3	3	1	1	1	..	..	..	..	10
82-85	..	4	2	4	1	...	1	1	1	..	..	..	..	15
78-81	..	2	2	3	5	3	7	3	1	1	..	1	..	28
74-77	..	1	3	4	6	5	3	2	1	..	..	1	..	26
70-73	..	1	2	5	7	8	6	5	1	1	..	..	1	36
66-69	..	2	9	15	5	8	6	5	1	..	..	..	..	54
62-65	1	4	6	13	13	7	9	3	..	..	..	..	..	56
58-61	..	1	3	9	11	5	3	2	2	1	..	1	1	39
54-57	1	1	...	7	3	4	3	1	..	..	..	..	..	20
50-53	1	...	...	3	1	1	3	..	2	..	..	..	..	11
46-49	1	...	...	3	1	...	..	1	..	..	..	..	..	6
Total	4	16	30	69	58	48	43	26	11	3	..	3	3	314

* r. = +0.100±0.013.
† r. = +0.100±0.020.
‡ r. = +0.205±0.022.
# r. = +0.179±0.036.
§ r. = +0.117±0.038.

ence can sometimes be accounted for solely by the fact that the persons in one group are heavier than those in the other.

We expected to find a somewhat better correlation between systolic blood pressure and the percentage of overweight or underweight, but we were disappointed. The coefficients for the younger and for the older men were in each case almost exactly the same as those obtained with the weights alone, unrelated to height.

The degree of overweight or underweight of the prisoners was measured also by means of the fulness index of Rohrer. Since the size of the body varies in three dimensions whereas height varies in only one, it has been thought best, when comparing height with weight, either to cube the one or else to extract the cube root of the other. Actually, in Rohrer's method, one divides the weight in kilograms by the cube of the height in centimeters.

Unfortunately, this index is affected not only by the amount of fat in the body but also by the relative length of the trunk and the legs. For this reason it is a better criterion of normal body weight in subjects of normal stature than in those who are short or tall. But even with this handicap the index correlated well with the figure expressing percentage of overweight or underweight. The coefficient was $+0.897 \pm 0.005$ for ages from 16 to 20, and $+0.923 \pm 0.005$ for ages from 30 to 33. The coefficient representing correlation between systolic blood pressure and the fulness index was, for ages from 20 to 39, $+0.104 \pm 0.012$ and for ages from 40 to 84, $+0.177 \pm 0.028$. Again, these figures are practically the same as those obtained with the weight uncorrected for height.

We could not demonstrate any correlation between blood pressure and height, or, during the early years of adult life, any correlation between blood pressure and surface area. During the later years of life, there appears to be a small positive correlation between systolic pressure and surface area. The coefficient was, for the ages from 20 to 25, $+0.072 \pm 0.020$ and for ages from 40 to 84, $+0.126 \pm 0.029$.

It has often been stated that hypertension occurs more often in the stocky, short-necked type of man than in the tall, thin, long-chested type, but so far as we know little work has been done to prove the point. Before we could make correlation tables we had to have some index of stockiness or ranginess, some figure to express numerically the relation between volume of trunk and volume or length of the lower limbs. After some investigation we chose the "pyknic index" which according to Wertheimer and Hesketh [18] is the most satisfactory of the various

18. Wertheimer, F. I., and Hesketh, F. E.: A Minimum Scheme for the Study of the Morphologic Constitution in Psychiatry, Arch. Neurol. & Psychiat. **17**:93 (Jan.) 1927.

indexes devised by anthropologists. It is obtained by substituting in the following formula:

$$\frac{\text{Leg length} \times 1{,}000}{\text{Transverse chest diameter} \times \text{sagittal chest diameter} \times \text{trunk height (to supra-sternal notch)}} \times 100$$

Using records of prisoners aged from 17 to 39 years, we could find no correlation between systolic pressure, and the "pyknic index." The coefficient was -0.089 ± 0.054. Apparently, then, there is little justification at present for the belief that there is a relation between body build and blood pressure.

TABLE 12.—*Systolic Blood Pressure of 442 Guards, All Weights*

Pressure in Millimeters	Age, Years				Total
	16-24	25-29	30-39	40-66	
90–99	1	..	2	3	6
100–109	5	4	20	8	37
110–119	4	12	28	30	74
120–129	3	13	46	40	102
130–139	4	12	29	40	85
140–149	4	2	19	33	58
150–159	2	1	5	28	36
160–169	..	1	4	12	17
170–179	..	..	..	12	12
180–189	1	..	..	6	7
190–199	..	..	1	5	6
200–209	..	..	..	1	1
210–219	..	..	..	..	...
220–229	..	..	..	..	...
230–239	..	..	..	1	1
Total	24	45	154	219	442
Mean	127.9	127.2	127.0	140.2	133.5
Standard deviation	20.9	12.2	15.8	22.9	20.8
Probable error of the mean	2.9	1.2	0.9	1.0	0.7
Median	126.7	125.0	125.9	137.1	130.2
Mode	124.2	120.6	123.6	131.0	123.8
Percentage above 140 mm.	29.2	8.9	18.8	44.8	31.3

Only one correlation coefficient was calculated for diastolic pressures and that was for diastolic pressure and the fulness index. For prisoners aged from 20 to 25 years there was no correlation.

STUDIES ON GUARDS

Table 12 and chart 6 summarize the measurements made on 442 guards. We were surprised to find their pressures so much higher than those of the prisoners. Some of the difference is probably due to the fact that the guards are considerably heavier than the prisoners. Unfortunately measurements of height and weight were not made when the guards were examined, and hence we cannot compute how much of the observed difference in pressure is due to the difference in weight.

We have already referred to the fact that the men whom we designate here as guards were examined at a time when they were applicants for the position, and when they were much concerned for fear that something would be found to cause their rejection. The prisoners naturally had no such worries and hence could look on the examination with only a mild interest. In trying to account for the large numbers of guards with hypertension, it must be remembered also that some of them would probably never have applied for a lazy man's job if they had not been somewhat unfit and doubtful of their ability to lead a normally strenuous and successful life.

It is remarkable that 29 per cent of the guards aged from 16 to 24 years and 44.8 per cent of those aged from 40 to 66 years showed pressures higher than 140 mm. of mercury. As will be remembered, the corresponding figures for the prisoners were much smaller.

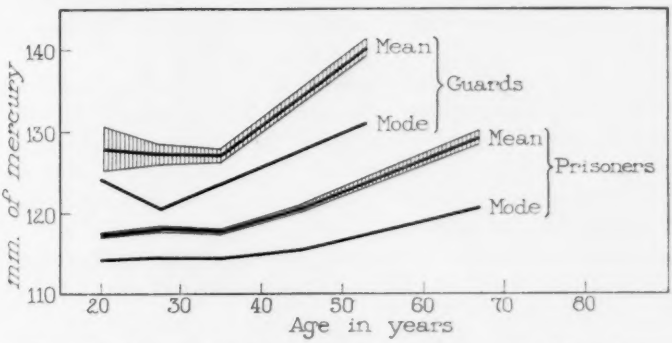

Chart 6.—Mean and modal systolic blood pressure of white prisoners and guards, of all weights. The shaded area represents the limits of probable error of the mean.

COMMENT

Again it has been demonstrated that the level of pressure in most persons does not rise even in old age. Many of those who are found to have hypertension during the fifth decade of life probably had it already by the end of the second. That this is true is suggested by the fact, already commented on, that the percentage of men with pressure levels higher than 140 mm. remains practically the same from the age of 15 until the age of 40 years. If during this time there were many accessions to the ranks of those with hypertension, one would expect this percentage to increase. It may be, however, that the mortality in this group is such that the losses balance the accessions.

We have been impressed by the fact that the level of blood pressure seems to be little affected by such factors as dissipation, the use of

alcohol and drugs, or even by so chronic an infection as syphilis. It appears to be affected largely by heredity, and it certainly is affected by excitement, nervous strain, the day's work, the amount of fat in the body and the temperature of the air.

SUMMARY

There is need for more knowledge about biologic variations in blood pressure in groups of men and women chosen at random from the nation.

In the prisoners studied, modal blood pressure varies but little from youth to old age. Mean pressure does not increase until after the age of 40 years. In the years from 20 to 40 the percentage of men with pressures higher than 140 mm. of mercury remains almost constant. This suggests that all those who have hypertension at the age of 40 had it at the age of 20. The percentage distribution polygons show that the lower limit of normal pressure is about 90 mm., whereas the upper limit is about 140 mm.

The modal or most typical pressure is the one which should be studied when one wants to know what normal blood pressure is. In the prisoners it is about 115 mm. of mercury. This is lower than the figure usually found for men out in the world. The reason may be that the prisoners are not fatigued and worried by the struggle to make a living; to a certain extent their pressures are basal.

It appears from this study that a pressure of 115 mm. is just as normal and a pressure of 140 mm. is just as abnormal in an old man as in a young one.

After the age of 35 years, fatness tends to increase blood pressure and thinness tends to decrease it.

The older Mexican prisoners rarely show the increase in blood pressure which is seen so commonly in natives and residents of the United States. In the older negroes, however, this increase is more than usually striking. It is absent in syphilitic prisoners.

Judging from this study, the use of alcohol has no effect on blood pressure. Drug addicts appear to have slightly increased blood pressures during the years of middle life. The use of tobacco by young men appears to raise the modal pressure about 4 mm. It does not appear to produce pathologic hypertension. Cool weather slightly raises the level of mean blood pressure.

The men convicted of murder in the first degree have a mean pressure 3 ± 1.2 mm. higher than that of other prisoners of like ages. Strange to say, those who only attempted murder or who were convicted of second degree murder have normal pressures.

Modal diastolic pressure is 68.5 mm. in the younger men, and 73 mm. in the older men. Diastolic pressure tends to rise several years earlier than systolic pressure. As a result, pulse pressure decreases during the fourth decade of life. Fatness and leanness have a slight effect on diastolic pressure.

In middle-aged men there is a slight correlation between systolic blood pressure and weight, and also between systolic pressure and surface area. There is no correlation with height or with the degree of stockiness or ranginess. Contrary, then, to the general impression, thick-set, stocky men are apparently no more likely to develop hypertension than are their tall, thin, asthenic-looking brethren.

The prison guards have pressures considerably higher than those of the prisoners. This may be due partly to overweight and partly to the fact that at the time the measurements were taken the guards were applying for a position, and many were anxious for fear something would be found to cause their rejection.

THE METABOLISM OF OBESITY

VII. THE AFTER-EFFECT OF MUSCULAR EXERCISE ON THE PRODUCTION OF BASAL HEAT *

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It has been a question in the minds of many clinicians and investigators whether the thirty minute rest period commonly used before basal metabolic tests served as sufficient time for the body to come to basal conditions especially in the case of patients who come from a distance. Benedict and Crafts [1] demonstrated that after a thirty minute rest the energy metabolism of normal women was only slightly increased following muscular exercise consisting of the usual morning routine as compared with the test made after a night's rest in bed. The question arose whether these observations would be applicable to obese and underweight subjects, and further whether subjects who had more vigorous exercise would require a longer period of rest. The present investigation was therefore undertaken.

EXPERIMENTAL WORK

A total of forty-one experiments consisting of four tests each were conducted on thirty-five women, thirteen of whom were obese, fifteen normal and seven underweight. With the exception of two obese subjects, who were 55 and 56 years old, the group ranged from 18 to 31 years of age. The variation for the normal group was from 19 to 38 years, while that for the underweight group was from 20 to 38 years. The percentage deviations from the standard weight [2] ranged from + 85.1 to + 13.3 with an average of + 49.7 in the obese group. The corresponding values in the normal and underweight groups, respectively, were from + 8 to — 7.9 with an average of — 1.6, and from — 15.1 to — 26.4 with an average of — 20.7 per cent.

* Submitted for publication, Nov. 1, 1929.

* From the Medical Clinic, the Gusta Morris Rothschild Fund and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

1. Benedict, Francis G., and Crafts, Elizabeth E.: Is Prolonged Bed Rest a Prerequisite for the Measurement of Metabolism? Am. J. Physiol. **74**:369, 1925.

2. Association of Life Insurance Medical Directors and Actuarial Society of America, Medico Actuarial Mortality Investigation, 1912.

The production of heat was measured by the Tissot gasometer in connection with a Haldane gas analysis apparatus. The bicycle ergometer, which was described in one of our previous papers,[3] was employed for the measurement of muscular exercise. All the experiments were performed under a postabsorptive condition. Following a thirty minute rest period the basal test of ten minutes was taken; this was followed by another test made while the subject was riding the ergometer at a speed of about 120 revolutions per minute and with a load of about six pounds (2.7 Kg.). The period of exercise varied in length from three and five-tenths to six and two-tenths minutes depending on the subject's ability. The third and fourth tests were made fifteen and thirty minutes after the exercise.

COMMENT

A higher production of heat than the basal value was found in thirty of forty-one experiments made fifteen minutes after the exercise. The values are given in tables 1, 2 and 3. However, only thirteen were 10 per cent or more above the basal. Six of the thirteen were from the obese, two from the normal and five from the underweight group. The average differences from the basal value in the three groups were + 6.5, + 3.1 and + 6.8 per cent, respectively. The production of heat for all the subjects thirty minutes after exercising varied from + 10.5 to — 10.3 per cent from their basal value. Twenty-seven subjects showed a lower, eight a higher and six the same value as that fifteen minutes after exercising. No great difference from muscular exercise was observed in the recovery period in the three groups. The average variation from the basal value thirty minutes after the exercise was + 0.9, + 0.8 and — 0.1 per cent for the obese, normal and underweight subjects, respectively.

With the lowering of the production of heat there was a lowering of the respiratory quotient in all three groups. Thus the average respiratory quotients for the obese group were 0.759 for the basal value, 0.889 for the exercising, 0.822 fifteen minutes after the exercise and 0.748 thirty minutes after the exercise. The corresponding values for the normal group were 0.755, 0.921, 0.775 and 0.728, while those for the underweight group were 0.767, 0.971, 0.837 and 0.749. This variation in the respiratory quotient following exercise and subsequent rest periods is in agreement with that reported by Benedict and Cathcart [4] who found

3. Wang, Chi Che; Strouse, Solomon; and Morton, Zelma Owen: Studies on the Metabolism of Obesity: V. Mechanical Efficiency, Arch. Int. Med. **45**:727 (May) 1930.

4. Benedict, Francis G.; and Cathcart, Edward P.: Muscular Work. A Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine, Carnegie Institution of Washington, 1913, Bulletin 187.

TABLE 1.—*Heat Production Before and After Muscular Exercise in Obese Subjects*

				Weight		Basal Test			Exercising With Brake				15 Minutes After Exercise			30 Minutes After Exercise		
Subject	Sex	Age	Height	Kg.	Per Cent Difference from Normal	Respiratory Quotient	Calories per Hour Found	Benedict-Harris Difference, per Cent	Respiratory Quotient	Total Calories per Hour	Per Cent Difference from Basal	Work Done per Hour, Calories	Respiratory Quotient	Total Calories per Hour	Per Cent Difference from Basal	Respiratory Quotient	Total Calories per Hour	Per Cent Difference from Basal
H. B.	F	18	175.3	118.6	+85.1	0.765	84	— 4.6	0.836	379	+351.3	55	0.825	90	+ 7.1	0.739	82	— 2.4
H. B.	F	18	175.5	118.5	+84.3	0.765	82	— 2.7	0.864	365	+343.3	51	0.914	93	+13.4	0.789	89	+ 8.5
S. L.	F	32	145.0	92.6	+77.2	0.812	72	+ 3.8	0.974	417	+481.6	79	0.876	76	+ 5.6	0.746	70	— 2.8
E. H.	F	30	168.4	111.1	+73.4	0.817	73	— 7.8	0.908	343	+373.3	59	0.829	74	+ 1.4	0.777	72	— 1.4
E. H.	F	31	168.1	110.2	+72.0	0.691	77	— 1.4	0.865	326	+323.0	53	0.810	87	+13.0	0.691	79	+ 2.6
E. H.	F	31	167.9	105.4	+65.6	0.715	70	— 7.9	0.810	321	+357.2	55	0.886	80	+14.3	0.721	72	+ 2.9
L. K.	F	29	151.6	87.3	+64.1	0.795	63	— 7.7	0.940	351	+457.7	59	0.892	74	+17.5	0.744	62	— 1.6
M. C.	F	19	161.5	85.9	+54.9	0.665	74	+ 5.8	0.827	320	+330.2	57	0.771	79	+ 6.8	0.694	72	— 2.7
E. F.	F	23	166.1	85.7	+43.9	0.765	61	—13.2	0.864	322	+431.3	52	0.790	65	+ 6.6	0.755	66	+ 8.2
K. W.	F	19	160.8	78.5	+42.8	0.718	62	— 7.6	0.907	308	+395.1	47	0.706	62	± 0.0	0.714	60	— 3.2
E. F.	F	19	154.9	71.4	+37.7	0.762	58	— 9.4	0.906	295	+408.0	48	0.721	52	—10.3	0.707	52	—10.3
F. R.	F	35	151.4	69.2	+23.7	0.756	53	—10.9	0.912	309	+483.0	56	0.806	60	+13.2	0.787	57	+ 7.5
B. C. H.	F	56	156.2	77.0	+22.8	0.799	52	—12.6	0.907	256	+395.0	57	0.851	58	+11.5	0.807	57	+ 9.6
L. R.	F	56	154.4	72.0	+17.3	0.777	58	+ 2.1	0.902	260	+414.6	49	0.953	63	+ 8.6	0.757	55	— 5.2
T. A.	F	21	160.0	65.3	+16.8	0.762	57	— 7.0	0.842	267	+365.3	54	0.778	58	+ 1.8	0.793	63	+10.5
B. R.	F	20	156.7	61.3	+13.3	0.780	62	+ 3.1	0.906	286	+362.9	50	0.750	58	— 6.5	0.753	58	— 6.5
Average.....		28	160.8	88.1	+49.7	0.759	66	— 4.8	0.889	322	+392.0	55	0.822	70	+ 6.5	0.748	66	+ 0.9

TABLE 2.—*Heat Production Before and After Muscular Exercise in Normal Subjects*

				Weight		Basal Test			Exercising With Brake			Work Done per Hour, Calories	15 Minutes After Exercise			30 Minutes After Exercise		
Subject	Sex	Age	Height	Kg.	Per Cent Difference from Normal	Respiratory Quotient	Calories per Hour Found	Benedict-Harris Difference, per Cent	Respiratory Quotient	Total Calories per Hour	Per Cent Difference from Basal		Respiratory Quotient	Total Calories per Hour	Per Cent Difference from Basal	Respiratory Quotient	Total Calories per Hour	Per Cent Difference from Basal
E. B.	F	24	161.8	61.4	+8.0	0.758	57	— 3.8	0.993	302	+427.3	53	0.746	57	± 0.0	0.749	59	+3.5
D. T.	F	20	153.4	56.2	+6.6	0.778	53	— 8.6	0.983	263	+399.7	51	0.765	55	+ 3.8	0.749	55	+3.8
R. B.	F	26	158.8	57.6	+4.4	0.725	54	— 6.4	0.893	232	+332.0	59	0.773	48	—11.1	0.717	50	—7.4
N. H.	F	21	161.0	58.8	+4.2	0.743	50	—15.8	0.909	268	+440.0	51	0.764	52	+ 4.0	0.732	54	+8.0
E. M.	F	19	163.3	57.3	+1.6	0.776	58	— 1.7	0.918	261	+349.4	55	0.765	56	— 3.4	0.753	55	—5.2
I. G.	F	24	152.4	52.4	+0.2	0.760	50	— 8.2	0.862	223	+342.3	60	0.761	53	+ 6.0	0.748	52	+4.0
E. A. S.	F	27	164.6	59.4	—0.5	0.735	60	+ 2.3	0.855	237	+297.7	56	0.781	62	+ 1.7	0.621	60	±0.0
A. G.	F	19	151.4	50.3	—1.1	0.720	47	—14.3	0.786	222	+300.0	55	0.771	47	± 0.0	0.787	50	+6.4
M. W.	F	21	154.7	52.2	—1.9	0.767	55	— 2.5	0.807	285	+421.7	56	0.812	56	+ 1.8	0.736	58	+5.5
E. G.	F	19	160.7	53.6	—2.5	0.835	54	— 6.8	0.975	293	+448.5	55	0.786	54	± 0.0	0.802	54	±0.0
P. D.	F	38	153.4	55.0	—3.2	0.731	53	— 1.7	0.978	328	+522.7	57	0.774	60	+13.2	0.690	54	+1.9
V. A.	F	27	151.1	49.9	—6.2	0.789	53	— 4.7	0.964	296	+420.8	54	0.820	57	+ 7.5	0.672	48	—9.4
E. S.	F	19	154.9	48.3	—6.8	0.775	48	—11.6	0.972	268	+452.5	56	0.790	50	+ 4.2	0.747	50	+4.2
V. A.	F	27	152.4	50.0	—6.8	0.765	46	—14.8	1.000	267	+483.1	59	0.822	52	+13.0	0.649	45	—2.2
F. M.	F	19	160.5	51.2	—6.9	0.717	54	— 4.0	0.948	288	+433.8	55	0.731	57	+ 5.6	0.759	55	+1.9
F. M.	F	19	160.5	50.7	—7.8	0.717	54	— 4.0	0.908	284	+427.1	57	0.761	58	+ 7.4	0.751	54	±0.0
J. W.	F	35	172.1	63.2	—7.9	0.748	62	+ 5.7	0.909	294	+323.1	46	0.797	61	— 1.6	0.711	61	—1.6
Average....		24	158.0	54.4	—1.6	0.755	53	— 5.9	0.921	268	+404.7	55	0.775	54	+ 3.1	0.728	54	+0.8

TABLE 3.—*Heat Production Before and After Muscular Exercise in Underweight Subjects*

				Weight		Basal Test			Exercising With Brake			Work Done per Hour, Calories	15 Minutes After Exercise			30 Minutes After Exercise		
Subject	Sex	Age	Height	Kg.	Per Cent Difference from Normal	Respiratory Quotient	Calories per Hour Found	Benedict-Harris Difference, per Cent	Respiratory Quotient	Total Calories per Hour	Per Cent Difference from Basal		Respiratory Quotient	Total Calories per Hour	Per Cent Difference from Basal	Respiratory Quotient	Total Calories per Hour	Per Cent Difference from Basal
C. S.	F	21	162.3	48.6	—15.1	0.774	49	—10.4	0.979	264	+435.8	53	0.765	54	+10.2	0.752	52	+6.1
O. D.	F	25	157.7	46.6	—16.0	0.729	48	—10.3	0.865	230	+382.9	59	0.829	53	+10.4	0.000	44	—8.3
E. K.	F	38	160.0	48.8	—18.7	0.837	53	+ 2.8	0.902	230	+313.6	59	0.903	59	+11.3	0.756	51	—3.8
O. D.	F	25	158.2	45.4	—18.9	0.739	50	— 5.2	0.980	256	+413.7	54	0.727	48	— 4.0	0.772	49	—2.0
M. C.	F	25	159.0	44.1	—21.8	0.766	49	— 6.5	1.040	273	+458.7	63	0.827	55	+12.2	0.713	50	+2.0
M. B.	F	23	167.1	45.8	—23.7	0.809	57	+ 5.2	0.975	269	+374.1	56	0.916	64	+12.3	0.727	59	+3.5
V. S.	F	20	156.2	40.0	—25.4	0.749	54	+ 5.8	0.949	250	+360.4	49	0.740	54	± 0.0	0.753	52	—3.7
V. P.	F	25	159.0	41.5	—26.4	0.732	58	+ 9.4	0.987	281	+402.4	59	0.986	59	+ 1.7	0.904	55	—5.2
Average....		25	159.9	45.1	—20.7	0.767	52	— 1.2	0.971	255	+392.7	57	0.837	56	+ 6.8	0.749	52	—0.1

in most cases a high respiratory quotient during exercise and a decrease during the subsequent rest period.

Based on the observations in all three groups, a thirty minute period gave a satisfactory rest before a basal metabolic test following the muscular exercise. These results are in accordance with those found by Benedict and Crafts [1] in their study of normal subjects.

SUMMARY

A total of forty-one experiments consisting of four tests each were conducted on thirty-five women, thirteen of whom were obese, fifteen normal and seven underweight.

The average values for the production of heat fifteen minutes after muscular exercise were + 6.5, + 3.1 and + 6.8 per cent above the basal value for the obese, normal and underweight subjects, respectively.

The corresponding values thirty minutes after the exercise were + 0.9 and + 0.8 and — 0.1 per cent.

The lowered production of heat after exercise was accompanied by a lowered respiratory quotient.

Based on our observations, a thirty minute rest served as an adequate resting period for the measurement of the production of basal heat.

THE METABOLISM OF NORMAL AND LEUKEMIC LEUKOCYTES *

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It has been recognized for some time that leukocytes have a remarkable power of transforming dextrose into lactic acid [1] and that they consume a considerable amount of oxygen.[2] In normal blood, the leukocytes are present in such small numbers that their oxygen consumption is difficult to measure. The erythrocytes, enormously outnumbering them, also show a small but definite oxygen consumption.[3] The sugar consumption of normal blood is due in a large part to the erythrocytes.[4] When the number of white blood cells is increased, as in leukemia, the blood shows a greatly augmented consumption of oxygen,[5] and a rapid consumption of sugar,[6] due to the metabolism of the white blood cells. The metabolism of the blood platelets is comparatively insignificant because of their small size.

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* Submitted for publication, Nov. 22, 1929.

* Assistance has been given to us by Dr. George R. Minot.

* From the Thorndike Memorial Laboratory of the Boston City Hospital and the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University.

* A part of this work was done under a Bullard Fellowship of the Harvard Medical School (George Cheyne Shattuck Memorial Fellowship), and a part under a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1. Levene, P. A., and Meyer, G. M.: On the Action of Leucocytes on Glucose, J. Biol. Chem. **12**:265, 1912.

2. Grafe, E.: Die Steigerung des Stoffwechsels bei chronischer Leukämie und ihre Ursachen, Deutsches Arch. f. klin. Med. **102**:406, 1911.

3. Harrop, G. A., Jr.: The Oxygen Consumption of Human Erythrocytes, Arch. Int. Med. **23**:745 (June) 1919. Kawashima, Y.: Ueber die glykolytische Kraft des Blutes: III. Mitteilung. Untersuchungen über die Beziehung zwischen der glykolytische Kraft und der O_2-Zehrung der Erythrozyten, J. Biochem. **4**: 411, 1925.

4. Maclean, H., and Weir, H. B.: The Part Played by the Different Blood Elements in Glycolysis, Biochem. J. **9**:412, 1915.

5. Daland, G. A., and Isaacs, R.: Cell Respiration Studies: II. A Comparative Study of the Oxygen Consumption of Blood from Normal Individuals and Patients with Increased Leucocyte Counts (Sepsis; Chronic Myelogenous Leukemia), J. Exper. Med. **46**:53, 1927. Grafe (footnote 2).

6. Bürger, M.: Untersuchungen über Hämoglykolyse, Ztschr. f. d. ges. exper. Med. **31**:1, 1923. Maclean and Weir (footnote 4).

Warburg [7] and his associates have shown that it is possible to demonstrate fundamental differences of metabolism between cancer, embryonic and normal adult tissues by a study of their consumption of oxygen and of sugar under aerobic and anaerobic conditions. The white blood cells have been studied in this manner, and have been shown to have a metabolism different from that of almost all other normal tissues. Exudate leukocytes have been shown to resemble cancer in their metabolism,[8] while the metabolism of leukocytes from the blood and bone-marrow simulates closely that of embryonic tissues.[9] These investigations have all been confined to the leukocytes of lower animals and birds.

The metabolism of human leukocytes has also been studied, by somewhat different methods, however. In leukemic blood, the mature and immature leukocytes differ markedly as regards consumption of both oxygen and sugar. Daland and Isaacs [10] have shown that, other things being equal, the oxygen consumption of leukemic blood tends to be greater, the greater the percentage of mature leukocytes. On the other hand, Schmitz and Glover [11] demonstrated that the consumption of sugar tends to be less, the more mature the cells. Earlier work by Falcon-Lesses [12] was likewise suggestive of this fact. A somewhat similar observation has been reported by Tamiya and by Hawkins,[13] who found that the anaerobic sugar consumption of liver tissue (of chickens) decreases as the animal grows from the embryonic stage to maturity.

A more extensive study of the metabolism of normal and leukemic leukocytes has been undertaken and forms the subject of this paper. For the determination of sugar consumption, or glycolysis, suspensions of leukocytes have been used, thus eliminating the rather large and variable factor of sugar consumption by the erythrocytes and making it possible to calculate the sugar consumption of a given number or volume of leukocytes. This cannot be done in experiments with whole blood.

7. Warburg, O.: Ueber den Stoffwechsel der Tumoren, Berlin, Julius Springer, 1926.

8. Bakker, A.: Einige Uebereinstimmungen im Stoffwechsel der Carcinomzellen und Exsudatleukocyten, Klin. Wchnschr. **6**:252, 1927. Fleischmann, W., and Kubowitz, F.: Ueber den Stoffwechsel der Leucocyten, Biochem. Ztschr. **181**:395, 1927.

9. Fujita, A.: Ueber den Stoffwechsel der weissen Blutzellen, Klin. Wchnschr. **7**:897, 1928. Fleischmann and Kubowitz (footnote 8, second reference).

10. Daland and Isaacs (footnote 5, first reference).

11. Schmitz, H. L., and Glover, E. C.: Glycolysis in Leukemic Blood, J. Biol. Chem. **74**:761, 1927.

12. Falcon-Lesses, M.: Glycolysis in Normal and Leukemic Blood, Arch. Int. Med. **39**:412 (March) 1927.

13. Tamiya, C.: Ueber den Stoffwechsel der Leber in verschiedenen Stadien ihrer Entwicklung, Biochem. Ztschr. **189**:175, 1927. Hawkins, J. A.: Metabolism of Liver Tissue from Rats of Different Ages, J. General Physiol. **11**:645, 1928.

Oxygen consumption, on the other hand, has been most successfully determined in whole blood, the oxygen consumption of the red blood cells being so small in comparison to that of the leukocytes that it can be neglected. It has also been determined in suspensions of white blood cells.

The purpose of this investigation was to answer two questions: 1. Does the metabolism of white blood cells, measured by improved quantitative methods, bear a definite relationship to the degree of maturity of the cells? 2. Does the metabolism of leukemic white blood cells differ from that of normal white blood cells as the metabolism of cancer tissue differs from that of normal tissue, thus giving evidence that leukemia is an essentially malignant disease?

MATERIAL AND METHODS

For the study of the oxygen consumption of the white blood cells, whole blood specimens from fourteen patients with myelogenous leukemia and eight patients with lymphatic leukemia have been employed. Suspensions of leukocytes from eighteen patients with myelogenous leukemia, ten patients with lymphatic leukemia, six patients with leukocytosis from various causes and seven normal persons have also been studied. In many cases a number of experiments were performed on successive blood specimens taken from the same patient at intervals of days or months.

For the study of sugar consumption, or glycolysis, suspensions of leukocytes in plasma have been prepared from the blood specimens of sixteen patients with myelogenous leukemia, fifteen patients with lymphatic leukemia and eleven persons with normal blood. Four patients having leukemia of an extremely acute type which could not be definitely classified were also studied. In one series of experiments the sugar consumption was determined during incubation at 37 C. without shaking. In a second series, the suspensions were gently shaken during the test period; oxygen consumption was also determined simultaneously, duplicate samples being used. In a third series, the sugar consumption was determined in the presence of 95 per cent oxygen and 95 per cent nitrogen, respectively, the conditions used by Warburg [7] and other recent investigators of tissue metabolism.

Preparation of Suspensions of Leukocytes in Plasma.—The blood was withdrawn from an arm vein and immediately mixed with a small amount of a 2 per cent solution of heparin in 0.9 per cent sodium chloride (from 0.2 to 0.4 cc. per ten cubic centimeters of blood) to prevent clotting. The syringe was also wet with a small amount of the same solution before the blood was taken. In most cases the blood was then placed in long narrow test tubes (195 by 12 mm.) and centrifugated at low speed (from 1,200 to 1,400 revolutions per minute) for from ten to fifteen minutes, thus producing a layer of white blood cells above the mass of red blood cells. In case the separation was unsatisfactory, the upper layer of mixed white and red blood cells was pipetted off, resuspended in plasma and again centrifugated at low speed. Occasionally this procedure had to be repeated two or three times in order to obtain a suspension of leukocytes comparatively free from red blood cells. In making the suspensions, no Ringer's or citrate solution was employed, the blood plasma being used to dilute the cells to whatever volume was desired.

When the leukocyte count was low, separation was facilitated by centrifugation in tubes having a narrow neck at the point where the white blood cell layer

formed, the result being a thick layer of small diameter instead of a thin film spread out over the top of the red blood cell layer. This method has also been used by Endres.[14] During the course of the investigation, it was found that in most leukemic blood specimens the white blood cells can be separated satisfactorily without centrifugation, simply by allowing the blood to stand in small test tubes (100 by 10 mm.) for an hour or less. This method has been used in the preparation of a few of the suspensions.

No precautions were taken to keep the blood and cell suspensions sterile, since there is abundant evidence[15] that during short periods of incubation there is not enough bacterial growth in freshly drawn blood to have any appreciable effect on the metabolism.

The Determination of Number, Total Volume, Cell Size and Dry Weight of the Leukocytes.—The number of white blood cells and red blood cells per cubic millimeter of suspension was determined by counting. The percentage volume of the cells was found by means of a long narrow hematocrit tube (175 by 6.5 mm.), having a volume of 1 cc. and graduated in 0.01 cc. divisions. A cell volume as low as 1 per cent could be determined by means of this tube. Centrifugation was at the rate of 2,000 revolutions per minute for one-half hour.

The volume of the white blood cells was found by subtracting from the total cell volume the volume of the red blood cells. The latter was estimated from the red blood cell count by a simple calculation, it being assumed that 5,000,000 red bood cells have a volume of 45 per cent. This assumption is accurate enough for practical purposes when the number of red blood cells is comparatively small, as in our suspension.

By dividing the white blood cell volume, expressed in cubic millimeters per hundred cubic centimeters of suspension, by the cell count per cubic millimeter, a figure is obtained which represents the average cell volume. This figure is actually the volume of 100,000 white blood cells, and has been utilized for simplicity rather than the figure for the volume of a single cell.

Warburg and other recent investigators have expressed their results in terms of dry weight of tissue used. This has been done in a large number of the experiments of the present series. The dry weight of the leukocytes has been calculated as equal to one-fifth the volume.[16] The direct determination of the dry weight of leukocytes suspended in plasma is difficult, since the weight may easily be altered during the process of washing them free from plasma.

In studying the metabolism of white blood cells in suspension, the blood platelets present have been neglected because, although their oxygen and sugar consumption per milligram are fairly large, as shown later in table 12, the total amount of these is insignificant on account of the small volume of the platelets (0.001 c. mm. per hundred thousand platelets). The volume of 100,000 blood platelets is equaled by that of only 1,300 normal white blood cells.

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14. Endres, G.: Ein Verfahren zum Anreichern von weissen Blutkörperchen und Blutplättchen aus kleineren Blutmengen, Klin. Wchnschr. **6**:1407, 1927.

15. Macleod, J. J. R.: Blood Glycolysis: Its Extent and Significance in Carbohydrate Metabolism: The Supposed Existence of "Sucre Virtuel" in Freshly Drawn Blood, J. Biol. Chem. **15**:497, 1913. Tolstoi, E.: Glycolysis in Bloods of Normal Subjects and of Diabetic Patients, J. Biol. Chem. **60**:69, 1924. Cajori, F. A., and Crouter, C. Y.: A Comparison of the Rate of Glycolysis in Different Bloods with Special Reference to Diabetic Blood, J. Biol. Chem. **60**:765, 1924.

16. Warburg, O.: Versuche an überlebendem Carcinomgewebe (Methoden), Biochem. Ztschr. **142**:317, 1923.

Classification of the Blood Specimens and Suspensions According to the Degree of Maturity of the Leukocytes.—The blood specimens and suspensions were divided into three groups, according to the degree of maturity of the leukocytes. Group I comprises the bloods with the most mature cells, group III the bloods with the most immature cells, and group II is intermediate. Such groups cannot be rigidly defined, because each blood specimen shows peculiarities of its own, and the number and character of both typical and atypical cells must be taken into consideration in judging the picture of cell maturity or immaturity presented by each specimen. Nevertheless, it is seldom difficult to decide in which of these three broad groups a given blood specimen belongs.

Dr. George R. Minot has examined most of the stained smears made from the samples of blood used and assisted us in classifying them.

The classification is similar to that which was used in a study of the glycolysis of leukemic blood,[11] but it has been changed in some respects, group III of the present series comprising blood specimens with more immature cells than in the previous one. The essential point in this grouping is to classify the specimens according to the predominating group of cells, as these will exert the chief influence on the rate of metabolism.

The classification for myelogenous leukemia is as follows:

Group I: Bloods in which polymorphonuclear cells and metamyelocytes predominate, more immature cells being present in relatively low percentage.

Group II: Bloods in which the striking feature is the presence of myelocytes of all ages; polymorphonuclear cells and myeloblasts may be present in small numbers.

Group III: Bloods in which the immaturity of the cells is extreme. Specimens in this group contain 50 per cent or more of myeloblasts and premyelocytes (myelocyte *A* of Sabin and her associates[17]). Many of the cells are abortive in character.

The classification for lymphatic leukemia is similar.

Group I: Bloods in which the white blood cells are mostly normal small lymphocytes.

Group II: Bloods containing many medium and large lymphocytes.

Group III: Bloods with chiefly lymphoblasts and atypical lymphocytes, together with a few medium and large lymphocytes.

The same classification was used in grouping the suspensions of white blood cells prepared from leukemic blood specimens.

The Determination of Oxygen Consumption.—Oxygen consumption was determined by means of the apparatus of Wilbur, Daland and Cohen.[18] This consists of a closed chamber containing the blood, connected with a water manometer and a potassium hydroxide absorption chamber, the whole being immersed in a water bath at 37 C. The air in the chamber with the blood is forced in and out of the potassium hydroxide absorption chamber, this procedure quickly freeing it from carbon dioxide. Thereafter, any change in the volume of the inclosed air, as registered by the manometer, is due to the consumption of oxygen by the blood

17. Cunningham, R. S.; Sabin, F. R., and Doan, C. A.: The Development of Leucocytes, Lymphocytes and Monocytes from a Specific Stem-Cell in Adult Tissues, Carnegie Institute of Washington, 1925, Pub. no. 361, p. 227.

18. Wilbur, B. C.; Daland, G. A., and Cohen, J.: Cell Respiration Studies: I. A Microspirometer for the Continuous Study of the Oxygen Absorption by Living Cells, J. Exper. Med. **46**:43, 1927.

cells. A compensation chamber is attached in such a way that slight changes in temperature do not affect the reading of the manometer. A stirring device is also provided, which keeps the blood cells in gentle motion and prevents them from settling.

In the use of this apparatus certain points must be kept in mind. If whole blood is being studied, the red blood cells must first be fully saturated with oxygen, preferably before being introduced into the apparatus, in order that the taking up of oxygen by hemoglobin may not be confused with actual oxygen consumption by the cell protoplasm. In the case of blood specimens having a large number of actively respiring leukocytes, it is impossible for the blood to absorb oxygen fast enough to supply their needs, even if fairly vigorous stirring is employed. The result is that the red blood cells become partially desaturated, giving up their oxygen to the white blood cells. In such cases, which are not common, the observed oxygen consumption of the leukocytes is somewhat lower than the actual oxygen consumption since the oxygen abstracted from the red blood cells cannot be measured. In suspensions of white blood cells, the oxygen consumption is considerably lower than in specimens of whole blood containing a corresponding number of cells. This is caused, in part at least, by the fact that in the suspensions there are almost no red blood cells to take up oxygen and pass it along to the white blood cells. It is therefore advantageous to use whole blood rather than suspensions of leukocytes for the determination of oxygen consumption.

After the blood has been placed in the respiration chamber, a few minutes must be allowed for it to come to a relatively constant p_H. The free carbon dioxide present is rapidly abstracted, and at the same time the p_H rises. After this initial rise the p_H remains comparatively constant but tends gradually to fall again on account of the lactic acid which the white blood cells are constantly producing. The net result depends on the amount of lactic acid formed. The p_H, measured by the colorimetric method at the end of a number of the experiments, has varied between 7.6 and 8.3. Fortunately, such a variation has no great effect on the rate of oxygen consumption. Koehler and Reitzel,[19] studying the effect of p_H on the oxygen consumption of blood and various tissues, obtained figures indicating that at a p_H of 8.3 there is a diminution of about 15 per cent as compared with a p_H of 7.4. We have performed a number of experiments that have yielded results similar to theirs.

The oxygen consumption of the erythrocytes is so much smaller than that of the leukocytes, provided the number of leukocytes is not below 20,000 per cubic millimeter, that it may be neglected, even in whole blood, and the entire oxygen consumption of the blood attributed to the white blood cells.

The oxygen consumption, per hour, of the blood or suspension of leukocytes, expressed as cubic centimeters per hundred cubic centimeters, divided by the leukocyte count expressed in thousands per cubic millimeter, gives the oxygen consumption per hour in cubic centimeters per $1{,}000 \times 10^5$ leukocytes. The oxygen consumption per hour expressed as cubic millimeters per cubic centimeter of suspension, divided by the dry weight of the leukocytes in a cubic centimeter of suspension (calculated from the hematocrit reading and expressed in milligrams), gives the oxygen consumption per hour in cubic millimeters per milligram of leukocytes. The symbol "Q_{O_2}" is used by Warburg [7] to express this quantity.

The Determination of Sugar Consumption.—The experiments of the first series (tables 7, 8 and 9) were done by the following method. From 5 to 8 cc. of

19. Koehler, A. E., and Reitzel, R. J.: The Effect of p_H on the Oxygen Consumption of Tissues, J. Biol. Chem. **64**:739, 1925.

leukocyte suspension was placed in a 50 cc. Erlenmeyer flask. After the removal of a 1 cc. sample for the determination of the initial concentration of sugar, the flask was stoppered tightly with cotton, rapidly warmed to 37 C. in a bath of warm water and then placed in an incubator at 37 C. Thereafter, 1 cc. samples were withdrawn for sugar determinations at one-half or one hour intervals, the protein-free filtrate being immediately prepared from each sample as soon as taken. The blood was not shaken, except when samples were removed for analysis. Protein-free filtrates were made by the method of Folin and Wu,[20] and sugar was determined by the method of Folin.[21]

The experiments of the second series (table 10) were performed in a similar manner except that the cells were kept in gentle motion by a device which tipped the containers from side to side about once in three seconds. Oxygen consumption was also determined simultaneously, with duplicate samples of suspension, by the method already described. Some of the sugar determinations were made by the method of Folin,[21] and the remainder by the method of Folin and Wu.[22]

In the third series (table 11), the sugar consumption was determined under "aerobic" and anaerobic conditions as used by Warburg, that is, in 95 per cent oxygen and 95 per cent nitrogen, respectively. Three or 4 cc. of leukocyte suspension was placed in a specially designed vessel having an inlet and an outlet tube, with stopcocks, so that the air within could be washed out and replaced by the gas mixture, the stopcocks being then closed so as to retain this. For aerobic conditions a mixture of 95 per cent oxygen and 5 per cent carbon dioxide was used; for anaerobic, 95 per cent nitrogen and 5 per cent carbon dioxide. The carbon dioxide in these mixtures served to keep the blood carbon dioxide at a physiologic level. The gas was passed through the chambers at a rapid rate for about five minutes to insure that the air was thoroughly washed out. The chambers were then placed in a water bath at 37 C. and allowed to remain there with gentle shaking for from forty to sixty minutes. Sugar determinations were done at the beginning (before the chambers were filled with gas), and again at the end of the experiment. In calculating the rate of sugar consumption, only the time while the chambers were in the water bath was used; the small amount of sugar consumption at room temperature during the filling of the chambers with gas mixture could be neglected. In order to prevent the sugar from being entirely used up during the course of the experiment, a small amount of pure dextrose (about 100 mg. per hundred cubic centimeters) was added to the suspension and thoroughly dissolved, a short time before the initial sample was taken for sugar determination. It was shown by control experiments (to be described) that this procedure did not affect the rate of sugar consumption.

The sugar consumption, per hour, expressed as milligrams of dextrose per hundred cubic centimeters, divided by the leukocyte count expressed in thousands per cubic millimeter, gives the sugar consumption per hour in milligrams per $1{,}000 \times 10^5$ leukocytes. The sugar consumption per hour, expressed as milligrams per hundred cubic centimeters, divided by the dry weight of leukocytes in 100 cc. of suspension (calculated from the hematocrit reading and expressed in milli-

20. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**: 81, 1919.

21. Folin, O.: The Determination of Sugar in Blood and in Normal Urine, J. Biol. Chem. **67**:357, 1926. Folin, O., and Svedberg, A.: The Sugar in Urine and in Blood, J. Biol. Chem. **70**:405, 1926.

22. Folin, O., and Wu, H.: A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

grams), gives the sugar consumption in milligrams per milligram of leukocytes per hour.

A small fraction of the sugar utilized by the cells is probably oxidized. The remainder is converted into lactic acid,[23] a process requiring no oxygen. The term "glycolysis" is applied, in its narrower sense, only to the latter process. In most of the experiments the total sugar consumption has been determined, but in the series reported in table 10 the glycolysis has been calculated by deducting from the total sugar consumption the amount of sugar oxidized, it being assumed that all the oxygen consumed was used for this purpose. The amount oxidized is found by simple chemical calculation to be 0.00133 Gm. of dextrose per cubic centimeter of oxygen consumed. The glycolysis thus determined is on the average about 85 per cent of the total sugar consumption.

RESULTS

Oxygen Consumption.—The amount of oxygen consumed by blood from normal persons is so small that it cannot be measured satisfactorily by the methods used. This is due to the fact that the oxygen consumption of the red blood cells is extremely small, while the white blood cells, though actively respiring, are comparatively few in number. The results on twenty-two normal blood specimens are reported in a previous paper.[10] Studies of blood specimens with increased white counts show that these have a considerably larger oxygen consumption. Several observations have been reported [10] in the case of a patient with polymorphonuclear leukocytosis accompanying an infected tumor growth. The average amount of oxygen consumed by the blood from this case was 0.09 cc. per $1{,}000 \times 10^5$ white blood cells per hour.

The results of observations on blood specimens from cases of myelogenous and lymphatic leukemia are given in tables 1 and 2. As in leukocytosis, the oxygen consumption of the blood is due almost entirely to the white blood cells, that of the red blood cells being negligible in comparison. The data are arranged according to the maturity of the white blood cells. Some of the results recorded in table 1 (marked by an asterisk) were reported before,[10] but not with the present method of grouping.

A study of the metabolism of blood from cases of myelogenous leukemia (table 1) shows that the more mature white blood cells have a higher rate of oxygen consumption than the immature cells. In group I, the most mature group, polymorphonuclear leukocytes and metamyelocytes were the predominating cells. The values for oxygen consumption ranged from 0.155 to 0.084 cc. per $1{,}000 \times 10^5$ white blood cells per hour. In group II, the intermediate group, the oxygen consumption ranged from 0.079 to 0.041 cc. In group III, characterized by the extreme immaturity of the white blood cells, the values were lowest of all, from 0.049 to 0.035 cc. The average rates for the three groups were 0.101, 0.060 and 0.043 cc., respectively. Thus there was

23. Fleischmann and Kubowitz (footnote 8, second reference).

a definite correlation between the maturity of the white blood cells and their rate of oxygen consumption.

The cases in group III merit further description on account of their unusual interest. The patients R. T. and L. S. were in a period of acute exacerbation marking the terminal stages of the disease, the duration of which was known to have been at least two and one-half years and one and one-half years, respectively. The blood of R. T., at this time, showed more than 50 per cent myeloblasts, many of which were atypical. Many megakaryocytes were present, with masses of blood platelets. The blood of L. S. showed 52 per cent myeloblasts and 42 per cent myelocytes; many of the latter were very young. There

TABLE 1.—*Oxygen Consumption of Blood in Myelogenous Leukemia*

Patient	Date	White Blood Cells per C.Mm.	Red Blood Cells per C.Mm.	Oxygen Consumed per Hour per 100 Cc. of Blood, Cc.	Oxygen Consumed per Hour per $1,000 \times 10^3$ White Blood Cells, Cc.	Degree of Maturity of White Blood Cells, Group*
W. D.	9/29/28	63,000	4,400,000	9.76	0.155	I
A. N.	9/20/28	48,000	4,000,000	4.90	0.102	I
K. G.*	1/12/26	80,000	4,000,000	6.46	0.081	I
C. L.*	10/ 5/26	53,000	3,800,000	3.84	0.072	I
F. N.*	12/17/25	37,000	2,800,000	4.48	0.121	I
G. S.*	12/18/25	123,000	3,100,000	12.67	0.103	I
S. L.*	12/12/25	71,000	2,200,000	6.14	0.086	I
W. D.	12/15/29	91,000	2,800,000	7.66	0.084	I
				Average	0.101	
S. L.*	12/ 8/25	122,000	3,200,000	9.72	0.079	II
P. S.	9/13/28	128,000	3,400,000	8.56	0.067	II
S. H.	9/25/28	200,000	3,500,000	11.71	0.059	II
F. N.*	4/ 7/26	112,000	4,100,000	5.89	0.053	II
S. H.*	10/13/26	454,000	3,000,000	18.56	0.041	II
				Average	0.060	
W. G.	12/ 8/28	210,000	3,600,000	9.42	0.045	III
B. O.	7/ 9/29	49,000	2,800,000	2.38	0.049	III
R. T.*	10/21/26	176,000	3,100,000	7.30	0.041	III
L. S.*	2/ 4/26	251,000	2,900,000	8.77	0.035	III
				Average	0.043	

* For explanation of group see text.

were practically no blood platelets. W. G. had a much more acute type of the disease. He had had symptoms for only six weeks prior to the date of the test. The differential count of the white blood cells showed 10.5 per cent polymorphonuclear cells, 30 per cent myelocytes and 62.5 per cent of primitive white blood cells or myeloblasts. Patient B. O. had a lower count than the others, but between 70 and 80 per cent of the cells were myeloblasts. Many of these were pathologic forms with vacuoles. A specimen submitted to the oxidase stain showed some granular cells, but these were hard to demonstrate either with Wright's stain or by supravital studies.

In lymphatic leukemia, as in myelogenous leukemia, the blood specimens with mature cells showed a much greater oxygen consumption

TABLE 2.—*Oxygen Consumption of Blood in Lymphatic Leukemia*

Patient	Date	White Blood Cells per C.Mm.	Red Blood Cells per C.Mm.	Oxygen Consumed per Hour per 100 Cc. of Blood, Cc.	Oxygen Consumed per Hour per $1,000 \times 10^3$ White Blood Cells, Cc.	Degree of Maturity of White Blood Cells, Group
C. O.	11/ 8/28	53,000	4,100,000	6.0	0.113	I
L. G.	7/19/28	58,000	3,200,000	6.2	0.107	I
K. N.	2/11/29	156,000	2,700,000	6.2	0.040	I
				Average	0.087	
R. N.	10/ 3/28	91,000	4,600,000	5.4	0.059	II
W. Y.	12/ 3/28	109,000	3,200,000	5.7	0.052	II
M. T.	12/ 7/28	172,000	1,200,000	8.8	0.051	II
				Average	0.054	
T. R.	7/ 8/29	.....	3,300,000	0.95	0.013	III
G. N.	5/ 7/29	75,000	1,300,000	0.85	0.011	III
				Average	0.012	

TABLE 3.—*Oxygen Consumption of Suspensions of White Blood Cells from Cases of Myelogenous Leukemia*

Patient	Date	White Blood Cells per C.Mm.	Volume of White Blood Cells, per Cent	Red Blood Cells, per C.Mm.	Oxygen Consumed per Hour per 100 Cc. of Suspension, Cc.	Oxygen Consumed per Hour per $1,000 \times 10^3$ White Blood Cells, Cc.	Oxygen Consumed per Hour per Mg. of White Blood Cells, C.Mm.	Degree of Maturity of White Blood Cells, Group
G. S.	7/20/26	115,000	9.6	65,000	2.72	0.024	1.4	I
S. S.	3/21/28	112,000	5.8	154,000	2.99	0.027	2.6	I
W. H.	9/27/27	222,000	15.0	270,000	5.24	0.024	1.8	I
S. L.	7/14/27	134,000	7.9	224,000	5.62	0.042	3.6	I
					Av.	0.029	Av. 2.3	
S. S.	3/23/28	121,000	6.8	273,000	5.09	0.042	3.7	II
S. L.	11/26/26	165,000	....	137,000	4.99	0.030	...	II
S. L.	12/13/26	232,000	....	121,000	3.95	0.017	...	II
S. A.	12/ 8/27	89,000	4.7	380,000	1.90	0.021	2.0	II
E. N.	11/23/26	265,000	....	80,000	3.68	0.014	...	II
A. Y.	9/22/27	274,000	....	256,000	6.99	0.026	...	II
M. S.	7/22/28	180,000	13.6	25,000	6.23	0.035	2.3	II
G. L.	9/20/27	171,000	12.2	260,000	4.99	0.029	2.1	II
M. K.	7/15/27	703,000	32.6	426,000	7.04	0.010	1.1	II
S. H.	10/15/26	74,000	8.6	140,000	3.63	0.049	2.1	II
S. H.	5/27/27	477,000	....	.....	4.99	0.010	...	II
S. H.	12/ 2/27	86,000	5.5	214,000	0.95	0.011	0.9	II
B. M.	3/15/28	100,000	7.0	103,000	5.71	0.057	4.1	II
H. Y.	10/18/28	136,000	9.7	35,000	2.38	0.018	1.2	II
					Av.	0.026	Av. 2.2	
P. W.	3/ 7/28	247,000	9.0	26,000	5.24	0.021	2.9	III
P. T.	7/21/27	124,000	9.4	90,000	5.33	0.043	2.8	III
R. T.	12/16/26	255,000	....	86,000	4.54	0.018	...	III
R. N.	10/ 8/27	125,000	3.7	44,000	3.90	0.031	5.3	III
R. N.	11/ 1/27	110,000	4.8	39,000	3.57	0.032	3.7	III
C. Y.	2/23/28	99,000	6.9	84,000	2.19	0.022	1.6	III
					Av.	0.027	Av. 3.2	

than those with many immature cells, as shown in table 2. In group I, two cases showed very high rates, 0.113 and 0.107 cc., respectively, per $1,000 \times 10^5$ white blood cells per hour. These were about twice the values in the intermediate group (0.059, 0.052 and 0.051 cc.) and nearly ten times the values for the bloods of group III, with many very immature cells (0.013 and 0.011 cc.).

The cases in group III deserve comment. The differentiation between very immature cells of the lymphatic and myelogenous types is

TABLE 4.—*Oxygen Consumption of Suspensions of White Blood Cells from Cases of Lymphatic Leukemia*

Patient	Date	White Blood Cells per C.Mm.	Volume of White Blood Cells, per Cent	Red Blood Cells, per C.Mm.	Oxygen Consumed per Hour per 100 Cc. of Suspension, Cc.	Oxygen Consumed per Hour per $1,000 \times 10^5$ White Blood Cells, Cc.	Oxygen Consumed per Hour per Mg. of White Blood Cells, C.Mm.	Degree of Maturity of White Blood Cells, Group
K. N.	7/11/27	290,000	6.7	30,000	4.76	0.016	3.6	I
B. N.	4/22/27	1,618,000	....	92,000	4.99	0.003	...	I
B. N.	5/17/27	971,000	....	14,000	5.67	0.006	...	I
B. N.	7/20/27	151,000	3.7	58,000	4.52	0.030	6.1	I
B. N.	6/27/28	232,000	5.3	192,000	6.90	0.030	6.5	I
B. N.	10/ 3/28	136,000	3.0	16,000	7.28	0.054	12.1	I
K. N.	4/20/27	354,000	....	24,000	2.67	0.008	...	I
B. S.	12/20/26	445,000	....	40,000	4.76	0.011	...	I
B. S.	12/22/26	241,000	....	8,000	2.72	0.011	...	I
A. G.	7/ 5/28	1,095,000	24.6	91,000	10.71	0.010	2.2	I
						Av. 0.018		
J. G.	4/16/28	680,000	14.6	21,000	6.90	0.010	2.4	II
G. R.	4/28/27	155,000	....	116,000	1.81	0.012	...	II
M. N.	4/21/27	177,000	....	92,000	2.13	0.012	...	II
M. N.	7/ 8/27	340,000	8.6	41,000	4.76	0.014	2.8	II
W. Y.	12/ 1/26	265,000	....	17,000	3.86	0.015	...	II
W. Y.	4/11/27	430,000	....	11,000	4.09	0.010	...	II
W. Y.	7/ 6/28	46,000	1.5	108,000	5.09	0.110	17.0	II
						Av. 0.026		
W. F.	7/20/28	298,000	12.2	142,000	6.80	0.023	2.8	III
W. F.	7/20/28	281,000	11.5	24,000	8.37	0.030	3.6	III
M. Y.	11/11/26	79,000	....	10,000	0.91	0.012	...	III
						Av. 0.022		

difficult, but in both cases (T. R. and G. N.) reported here the diagnosis of lymphatic leukemia was free from doubt. Both patients showed moderate enlargement of the lymph nodes as well as of the spleen and liver. Earlier observations had shown typical blood pictures of chronic lymphatic leukemia with many mature lymphocytes, but at the time of our experiments the cells were very immature, so that lymphoblasts and atypical large lymphocytes predominated. There was, in addition, a severe anemia and thrombopenia. Both patients died within a month after the tests reported here were made.

The values for oxygen consumption per $1,000 \times 10^5$ white blood cells averaged somewhat lower for the blood specimens of the patients with lymphatic leukemia than for those of the patients with myelogenous

leukemia. This difference was no doubt due to the smaller size of the lymphatic cells.

Suspensions of white blood cells in plasma were also used for the determination of oxygen consumption. The results obtained are shown in tables 3, 4 and 5. Cells from normal blood from patients with polymorphonuclear leukocytosis and from cases of myelogenous and lymphatic leukemia were studied in this way.

In tables 3 and 4 the suspensions are listed in groups according to the maturity of the cells, in the same manner as was done for the specimens of whole bloods recorded in tables 1 and 2. In contrast to the latter specimens, however, the suspensions showed no relationship

TABLE 5.—*Oxygen Consumption of Suspensions of Normal White Blood Cells*

Name	White Blood Cells, per C. Mm.	Volume of White Blood Cells, Per Cent	Red Blood Cells, per C. Mm.	Oxygen Consumption per Hour per 100 Cc. of Suspension, Cc.	Oxygen Consumption per Hour per $1,000 \times 10^6$ White Blood Cells, Cc.	Oxygen Consumption per Hour per Mg. of White Blood Cells C. Mm.
White Blood Cells from Normal Subjects						
W. S.	36,000	2.6	164,000	1.90	0.053	3.7
E. V.	28,000	2.9	207,000	2.86	0.102	4.9
E. S.	43,000	3.4	214,000	4.52	0.105	6.7
B. D.	28,000	2.8	432,000	2.95	0.105	5.3
H. S.	18,000	1.3	34,000	2.71	0.151	10.4
M. L.	19,000	1.9	487,000	3.76	0.198	9.9
					Av. 0.119	
White Blood Cells from Patients with Polymorphonuclear Leukocytosis						
B. R.	67,000	...	1,500,000	1.59	0.024	....
W. P.	113,000	...	1,055,000	4.54	0.040	....
C. N.	74,000	7.0	1,310,000	3.09	0.042	2.2
A. N.	42,000	...	388,000	2.72	0.065	....
H. T.	44,000	...	377,000	3.18	0.072	....
A. N.	70,000	...	730,000	6.81	0.097	....
P. O.	13,000	1.8	198,000	1.43	0.110	4.6
					Av. 0.064	

between the degree of maturity of the cells and the rate of oxygen consumption.

The rates of oxygen consumption by the cells in these suspensions were definitely lower than the rates obtained by the use of whole blood, as shown in table 6. The rates were about the same in the suspensions of white blood cells from myelogenous and lymphatic leukemia. Both were much lower (0.027 and 0.021 cc.) than the rates in suspensions of normal white blood cells (0.119 and 0.064 cc.).

There are several reasons that may account for the lower rates of oxygen consumption in cell suspensions than in whole blood and for the lack of correlation between the maturity of the cells and the oxygen consumption. In the first place, the white blood cells in the suspensions were not as well supplied with oxygen. In the specimens of whole blood, the red blood cells, with their strong affinity for oxygen, were constantly absorbing it from the air and thus keeping the blood saturated, except in a few cases in which the oxygen consumption of the

white blood cells was so rapid that even the red blood cells could not keep pace with it and became desaturated. It is evident that in suspension the supply of oxygen must have been much smaller. A few red blood cells were present in the suspensions, but their effect was apparently negligible, and the rates of oxygen consumption appeared in no way dependent on their number.

Slight degrees of injury due to manipulation of the cells for preparation of the suspensions probably exerted a marked effect on their oxygen consumption. Thus Fujita [9] noted that the oxygen consumption of leukocytes could be markedly lowered by centrifugation. It is of interest that the leukemic white blood cells, even of mature type, showed much lower rates than the normal white blood cells. This may have been due, in part at least, to a greater susceptibility of the leukemic cells to injury. Szilard [24] has shown that the fragility of leukemic white blood cells is greater than that of normal cells when incubated in serum or

TABLE 6.—*Rate of Oxygen Consumption*

	Average Rate per 1,000×10⁵ White Blood Cells	
Diagnosis	Whole Blood, Cc.	Suspension, Cc.
Normal	.....	0.119
Leukocytosis	0.09	0.064
Myelogenous leukemia	0.075	0.027
Lymphatic leukemia	0.056	0.021

plasma. The frequent occurrence of broken cells in smears of leukemic blood likewise indicates an abnormal degree of fragility.

In the preparation of the suspensions, the blood specimens were centrifugated slowly in order to reduce cell trauma to a minimum. Such cell suspensions have been observed to use oxygen continually at a constant rate for from four to five hours, a fact which indicates that the cells could not have been seriously injured. Furthermore, stained smears prepared from the suspensions at the end of the experiments showed the leukocytes to be in excellent condition, and supravital studies showed the polymorphonuclear cells still motile, although not as active as at the beginning of the experiments.

It seems evident, therefore, that a slight amount of manipulation can exert a profound effect on the oxygen consumption of the white blood cells.

Sugar Consumption.—It was necessary first to determine whether or not the amount of sugar present in the cell suspension had any effect on the rate of sugar consumption. Warburg [7] reported that in the case of tissues the concentration of sugar in the surrounding fluid exerts a marked influence on the rate of consumption. Conflicting

24. Szilard, P.: Studies on Leukemia: I. Concerning the Fragility of the White Blood Cells, Am. J. M. Sc. **173**:343, 1927.

results have been obtained with whole blood, some investigators [25] finding that the higher the sugar concentration the more rapidly it is destroyed, others [26] finding an opposite relationship, while the weight of opinion [27] is that the rate of consumption in blood is independent of the sugar concentration. Our own experiments with whole blood [11] were in agreement with the last view. Table 7 shows the results of four experiments in which varying amounts of pure dextrose were added to white blood cell suspensions and the rates of sugar consumption at the different concentrations compared. It was found that the added dextrose had practically no effect on the rate of consumption. Furthermore, in numerous experiments the rate was followed at successive half hour or one hour intervals and found to remain constant as long as there was any sugar left. The rate of sugar consumption is independent of the concentration of sugar, at least up to a concentration of 250 mg. per hundred cubic centimeters.

TABLE 7.—*Effect on Sugar Consumption of Varying the Initial Concentration of Sugar*

Patient	Type of Leukemia	Initial Sugar Concentration		Sugar Consumption per 100 Cc. of White Blood Cell Suspension per Hour	
		Suspension 1 Mg. per 100 Cc.	Suspension 2 Mg. per 100 Cc.	Suspension 1 Mg.	Suspension 2 Mg.
G. R.	Lymphatic	133	210	5	5
S. H.	Myelogenous	182	246	18	22
K. N.	Lymphatic	142	218	36	35
B. N.	Lymphatic	134	226	55	52

Another series of experiments was performed to determine whether the rate per $1,000 \times 10^5$ cells was the same in suspensions having a high cell count as in more dilute suspensions of the same cells. There was some possibility that crowding of the cells in the more concentrated suspensions might cause a falling off in the rate of sugar consumption. The results shown in table 8 demonstrate that this is not the case. In parallel suspensions varying from two to eight times in the concentration of cells the rates of sugar consumption per $1,000 \times 10^5$ cells were remarkably constant with but one exception.

As a result of these preliminary experiments it was believed that the rates of sugar consumption obtained with different suspensions might

25. Falcon-Lesses (footnote 12). Cajori and Crouter (footnote 15, third reference).

26. Levene, P. A., and Meyer, G. M.: The Action of Leucocytes on Glucose, J. Biol. Chem. **11**:361, 1912. Lemann, I. I., and Liles, R. T.: Glycolysis at Varying Blood Sugar Levels, J. Lab. & Clin. Med. **11**:339, 1926.

27. Denis, W., and Giles, U.: On Glycolysis in Diabetic and Non-Diabetic Blood, J. Biol. Chem. **56**:739, 1923. Macleod (footnote 15, first reference). Irving, J. T.: The Degradation of Glucose by the Blood Corpuscle of the Rabbit, Biochem. J. **20**:613, 1926.

be safely compared without the occurrence of any significant error due to varying concentrations of sugar or of cells.

Table 9 shows strikingly the relationship of the maturity of the white blood cells to the rate of sugar consumption. The experiments of this first series were done without agitation of the cells. Of the myelogenous cells, the most mature (group I) showed the lowest sugar consumption, from 0.16 to 0.39 mg. per $1,000 \times 10^5$ white blood cells per hour. Those of moderate immaturity (group II) showed higher rates, from 0.42 to 0.76 mg. per hour, while the most immature cells (group III) had by far the highest rate, 0.93 mg. per hour. Similar but much lower figures were obtained with the lymphatic white blood cells, ranging from 0.082 mg. per $1,000 \times 10^5$ cells per hour in group I to 0.256 mg. in group III. White blood cells obtained from normal blood were also studied in three experiments. Since these were mature

TABLE 8.—*Effect on Sugar Consumption of Varying the Concentration of White Blood Cells*

Patient	Type of Leukemia	White Blood Cells per C. Mm.			Sugar Consumption per $1,000 \times 10^5$ White Blood Cells per Hour	
		Suspension 1	Suspension 2	Ratio of White Blood Cell Counts	Suspension 1, Mg.	Suspension 2, Mg.
B. S.	Lymphatic	61,000	122,000	2.0	0.09	0.10
W. Y.	Lymphatic	74,000	148,000	2.0	0.13	0.13
B. N.	Lymphatic	299,000	749,000	2.5	0.08	0.07
G. D.	Myelogenous	39,500	239,000	6.0	0.55	0.42
G. B.	Lymphatic	23,500	141,000	6.0	0.17	0.15
S. H.	Myelogenous	23,500	188,000	8.0	0.77	0.76

cells, predominantly of the myelogenous type, it was expected that their rate of sugar consumption would resemble that of the most mature cells of myelogenous leukemia. Surprisingly enough, it was much higher, from 0.64 to 0.79 mg. per $1,000 \times 10^5$ cells per hour, being distinctly greater even than the average rate for the moderately immature myelogenous cells of group II.

A series of more elaborate experiments is reported in table 10. In these experiments the cells were kept in better equilibrium with the surrounding plasma by constant gentle agitation. Oxygen consumption was determined simultaneously with sugar consumption. The values for oxygen consumption have already been given in tables 3, 4 and 5, but are inserted in table 10 also, for purposes of comparison. It is to be noted that glycolysis, rather than total sugar consumption, is reported in table 10. The amount of sugar presumably oxidized has been subtracted from the total amount of sugar consumed, leaving the amount changed to lactic acid, or glycolized. The results given in tables 10 and 11 are expressed in milligrams of sugar per milligram of cells, instead of in milligrams per $1,000 \times 10^5$ cells. The results are

thus independent of the size of the cells, which is variable as shown in the column giving the volume of 10^5 white blood cells. Cells of both myelogenous and lymphatic type are listed together in order to bring out the fact that, so far as the evidence goes, the rates of glycolysis per milligram are approximately the same in both types of cells of the same degree of maturity. The lower rates shown in table 9 for cells of the lymphatic type were evidently due entirely to the smaller size of the cells. The white blood cells in group III (table 10) were taken from

TABLE 9.—*Sugar Consumption of White Blood Cells (First Series) 37 C., No Shaking*

Patient	Date	White Blood Cells, per C.Mm.	Red Blood Cells, per C.Mm.	Sugar Consumption per $1,000 \times 10^3$ White Blood Cells per Hour, Mg.	Degree of Maturity of White Blood Cells, Group
		Myelogenous Leukemia			
G. S.	7/19/26	159,000	170,000	0.16	I
S. L. (1)	11/26/26	104,000	28,000	0.20	I
S. L. (2)	9/ 3/26	72,000	40,000	0.39	I
S. H. (1)	10/16/26	308,000	225,000	0.42	II
F. N.	10/19/26	89,000	125,000	0.47	II
G. D. (1)	1/29/27	38,000	48,000	0.57	II
G. D. (2)	1/28/27	90,000	85,000	0.70	II
S. H. (2)	5/ 3/27	188,000	117,000	0.76	II
C. L.	12/23/26	20,000	2,000	0.93	III
		Lymphatic Leukemia			
B. N.	4/22/27	299,000	17,000	0.082	I
M. O. (1)	11/27/26	57,000	22,000	0.086	I
K. R. (1)	8/ 3/26	71,000	18,000	0.089	I
K. N. (1)	11/29/26	154,000	10,000	0.094	I
M. O. (2)	11/16/26	122,000	50,000	0.097	I
B. S.	12/22/26	122,000	4,000	0.102	I
K. N. (2)	4/20/27	325,000	22,000	0.109	I
K. R. (2)	7/26/26	212,000	55,000	0.113	I
W. Y.	12/ 1/26	148,000	12,000	0.125	I+
H. E.	7/21/26	30,000	65,000	0.147	I+
M. N.	9/24/26	98,000	14,000	0.159	II
G. R.	4/28/27	141,000	106,000	0.162	II
M. Y.	11/11/26	49,000	11,000	0.256	III
		Normal			
G. R. (1)	12/ 2/26	4,800	8,600	0.64	...
G. R. (2)	3/24/27	39,000	89,000	0.61	...
M. N.	4/ 5/27	48,000	90,000	0.79	...

patients having acute leukemia. They were for the most part very primitive cells, and it was impossible to determine with certainty whether they were of myelogenous or of lymphatic origin.

The inverse relationship of glycolysis to the maturity of the white blood cells is clearly shown in table 10, though some irregularities are to be noted. Thus the cells of patient S. S., in group I, showed a glycolysis as high as would be expected in group III. The rates for group II showed a remarkably wide range of variation, from 0.018 to 0.045 mg. of sugar per milligram of cells per hour. It has already been stated that the oxygen consumption, which shows a direct relationship to the maturity of the cells when determined in whole blood, shows no

such relationship when determined in suspensions of the white blood cells. This is apparently due to injury of the cells during centrifugation and other manipulations employed in preparing the suspensions. Probably the similar but much less marked variability in the glycolysis of suspensions of white blood cells is also due to slight but varying degrees of cell injury.

TABLE 10.—*Glycolysis and Oxygen Consumption of White Blood Cells (Second Series) 37 C., Gentle Agitation*

Patient	Date	Type of Leukemia	White Blood Cells per C. Mm.	Volume of 10^5 White Blood Cells, C. Mm.	Red Blood Cells per C. Mm.	Glycolysis per Mg. per Hour Mg.	Oxygen Consumption per Mg. per Hour C. Mm.	Degree of Maturity of White Blood Cells, Group
K. N.	7/11/27	Lymphatic	290,000	0.024	30,000	0.014	3.6	I
S. L.	7/14/27	Myelogenous	134,000	0.059	224,000	0.016	3.6	I
A. G.	7/ 5/28	Lymphatic	1,095,000	0.022	91,000	0.019	2.2	I
B. N.	6/27/28	Lymphatic	232,000	0.023	192,000	0.020	6.5	I
B. N.	7/20/27	Lymphatic	151,000	0.024	58,000	0.022	6.1	I
S. S.	3/21/28	Myelogenous	112,000	0.052	154,000	0.046	2.6	I
						Av. 0.023		
M. N.	7/ 8/27	Lymphatic	340,000	0.025	41,000	0.018	2.8	II
M. K.	7/15/27	Myelogenous	703,000	0.046	426,000	0.021	1.1	II
W. Y.	7/ 6/28	Lymphatic	46,000	0.033	108,000	0.024	16.9	II
O. L.	9/20/27	Myelogenous	171,000	0.072	260,000	0.025	2.1	II
J. G.	4/16/28	Lymphatic	680,000	0.022	21,000	0.030	2.4	II
B. M.	3/14/28	Myelogenous	100,000	0.070	103,000	0.042	4.1	II
M. S.	7/22/27	Myelogenous	180,000	0.076	25,000	0.045	2.3	II
						Av. 0.029		
H. S.	11/ 4/27	Acute, ? type	107,000	0.060	64,000	0.042±	....	III
P. W.	3/ 7/28	Acute, ? type	247,000	0.036	26,000	0.043	2.9	III
P. T.	7/21/27	Acute, ? type	124,000	0.076	90,000	0.044	2.8	III
C. A.	2/23/28	Acute, ? type	99,000	0.069	84,000	0.050	1.6	III
						Av. 0.045		
Subject			Normal White Blood Cells					
B. D.	6/19/28		28,000	0.102	432,000	0.027	7.0	
M. L.	6/21/28		19,000	0.098	487,000	0.032	9.9	
W. S.	6/22/28		36,000	0.073	164,000	0.042	3.7	
E. S.	6/26/28		43,000	0.080	214,000	0.037	6.7	
E. V.	6/28/28		28,000	0.104	207,000	0.039	4.9	
H. S.	6/29/28		18,000	0.074	34,000	0.031	10.4	
						Av. 0.035		

With but one exception, the rates of glycolysis for cells of group I were not above 0.022 mg. per hour, while the rates for group III were not below 0.042 mg. per hour.

The average rate of glycolysis for cells of group I was 0.023 mg. per milligram per hour, for group II, 0.029 mg. and for group III, 0.045 mg. The glycolysis of white blood cells obtained from normal healthy subjects was again surprisingly high, 0.035 mg., or distinctly above the average for cells from cases of myelogenous leukemia placed in group II.

In table 11 are shown the results obtained by measuring the sugar consumption of suspensions of white blood cells in 95 per cent oxygen and 95 per cent nitrogen respectively, the aerobic and anaerobic con-

ditions used by Warburg [7] and his collaborators and by Fujita.[9] White blood cells from patients with myelogenous and lymphatic leukemia and from persons with normal blood were thus tested. In 95 per cent nitrogen, the sugar consumption of the cells was about the same for all types of leukemic cases so that there was no relationship to the maturity of the cells. In 95 per cent oxygen, however, marked differences appeared. In the cases of myelogenous leukemia, the rates of sugar consumption were much higher for suspension containing chiefly mature cells. This is directly opposed to the results obtained when the cell suspensions were

TABLE 11.—*Sugar Consumption of White Blood Cells in Oxygen and in Nitrogen 37 C., Gentle Agitation*

Patient	Date	White Blood Cells per C.Mm.	Volume of 10^5 White Blood Cells, C.Mm.	Red Blood Cells per C.Mm.	Sugar Consumption per Mg. per Hour in 95% O_2, 5% CO_2, Mg.	Sugar Consumption per Mg. per Hour in 95% N_2, 5% CO_2, Mg.	Degree of Maturity of White Blood Cells, Group
			Myelogenous Leukemia				
P. S.....	11/23/28	91,000	0.036	23,000	0.103	0.073	I
W. D.....	12/15/28	68,000	0.082	40,000	0.066	0.079	I
S. G.....	3/22/29	198,000	0.069	42,000	0.056	0.068	II
B. D.....	1/../29	442,000	0.074	156,000	0.030	0.033	II
W. G.....	12/ 8/28	189,000	0.051	43,000	0.013	0.059	III
W. G.....	12/11/28	121,000	0.046	5,000	0.013	0.082	III
W. G.....	1/ 3/29	197,000	0.045	700,000	0.011	0.063	III
B. O.....	7/10/29	71,000	0.054	6,000	0.008	0.079	III
			Lymphatic Leukemia				
K. N.....	2/11/29	179,000	0.023	.....	0.009	0.059	I
W. Y.....	12/ 3/28	111,000	0.026	12,000	0.000	0.067	II
M. T.....	12/ 7/28	107,000	0.012	44,000	0.016	0.081	II
G. N.....	5/ 7/29	69,000	0.029	13,000	0.000	0.057	III
T. R.....	7/ 8/29	221,000	0.028	172,000	0.012	0.070	III
			Normal				
M. Y.....	1/ 2/29	64,000	0.061	185,000	0.054	0.046	...
J. S.....	5/ 9/29	22,000	0.047	40,000	0.052	0.052	...
S. I.....	5/15/29	34,000	0.035	48,000	0.060	0.067	...

exposed to air. In the cases of lymphatic leukemia the cells of all degrees of maturity, even including the mature lymphocytes of case K. N., showed a very low sugar consumption in the presence of 95 per cent oxygen. Three suspensions of white blood cells from patients with normal blood showed a behavior similar to that of the more mature cells from cases of myelogenous leukemia, in that the rates of sugar consumption were about the same in both oxygen and nitrogen.

The metabolism of blood platelets was also studied in a suspension containing 1,001,000 blood platelets per cubic millimeter, and only 3,000 white blood cells and 1,500 red blood cells per cubic millimeter. This suspension was prepared from the blood of a patient with myelogenous leukemia with an exceptionally large number of blood platelets. Glycolysis was determined in air and in pure nitrogen, conditions

similar to those used by Endres and Kubowitz [28] for the study of blood platelets. In table 12 our results are compared with those of Endres and Kubowitz for the blood platelets of human beings and with those of Fujita [9] for the blood platelets of rats. Our figures do not show the marked difference between aerobic and anaerobic glycolysis which they found, the metabolism being similar to that of normal white blood cells.

COMMENT

The foregoing results indicate a definite relationship between the metabolism of white blood cells from cases of leukemia and the degree of their maturity. As the cells develop from primitive types to adult forms, the consumption of oxygen becomes steadily greater, while the transformation of dextrose into lactic acid becomes correspondingly less. The white blood cells are susceptible to injury, so that in the process of separating them from the red blood cells by centrifugation their oxygen consumption, and, to a lesser degree, their sugar consumption is altered. For this reason the correlation between oxygen consumption and the age of the cells is not demonstrable by a study of cell suspensions but only by observations on cells in whole blood; likewise, the correlation between sugar consumption and maturity though clearly indicated is not perfect in cell suspensions.

TABLE 12.—*Glycolysis and Oxygen Consumption of Blood Platelets*

Authors	Aerobic Glycolysis per Mg. per Hour, Mg.	Anaerobic Glycolysis per Mg. per Hour, Mg.	Oxygen Consumption per Mg. per Hour, C.Mm.	Volume of 10^3 Platelets, C.Mm.
Glover, Daland and Schmitz	0.040	0.058	7.5	0.001
Endres and Kubowitz [28]	0.021	0.084	8.4	.....
Fujita [9]	0.004	0.100	6.2	.....

Many of the patients whose blood was studied had received high voltage (170,000 volts) roentgen treatments at times varying from days to months previous to our tests. Blood was not taken during the first few hours after treatment, but after this period the metabolism of the cells appeared to be no different from that of cells of the same degree of maturity from untreated patients.

There is no fundamental difference between the metabolism of leukemic white blood cells and that of normal white blood cells. The normal cells, however, show a more active metabolism than do cells of corresponding maturity in leukemic blood, as regards both oxygen and sugar consumption.

28. Endres, G., and Kubowitz, F.: Stoffwechsel der Blutplättchen, Biochem. Ztschr. **191**:395, 1927.

Warburg [7] has demonstrated important differences in the metabolism of different types of tissue, which may be summarized as follows:

	Oxygen Consumption	Aerobic Glycolysis	Anaerobic Glycolysis
Normal adult tissue	Moderate	Small	Small
Embryonic tissue	Moderate	Small	Large
Malignant tumors	Moderate	Large	Large

He and others have recognized that this classification is not absolute, the most notable exceptions being the retina and the white blood cells.[29]

Furthermore, there is considerable variation in the metabolic activity even of tumors. Some malignant tumors, for example, have a metabolism similar to that of benign tumors, according to Warburg's classification, as demonstrated by Murphy and Hawkins.[30] Hawkins [31] concluded that the anaerobic glycolytic activity of tissues is a function of their growth rate.

Typical results obtained by other investigators for the metabolism of leukocytes are given in table 13. The figures for glycolysis have

TABLE 13.—*Metabolism of Leukocytes as Determined by Other Investigators*

Authors	Description of Leukocytes	Oxygen Consumption per Mg. per Hour, C.Mm.	Aerobic Glycolysis per Mg. per Hour, Mg.	Anaerobic Glycolysis per Mg. per Hour, Mg.
Bakker [29]	Exudate leukocytes of rabbits	0.4	.....	0.017
Fleischmann and Kubowitz [23]	Exudate leukocytes of rabbits	4.5	0.056	0.084
	Blood leukocytes of geese	4.4	0.007	0.046
Fujita[9]	Blood leukocytes of rats	9.1	0.009	0.082
	Bone-marrow cells of rats	9.8	0.015	0.084

been recalculated from the original figures, in which the amount of glycolysis was represented by the volume of carbon dioxide liberated by the formation of lactic acid. The results obtained by Bakker were much lower than the rest. The metabolism of exudate leukocytes obtained from rabbits by Fleischmann and Kubowitz [23] resembled that of malignant tissue, whereas the metabolism of blood leukocytes of geese and of rats and of bone-marrow cells of rats resembled that of embryonic tissue. The results of our own experiments under aerobic and anaerobic conditions (table 11) interpreted in the same way are as follows: Normal white blood cells and mature cells from cases of myelogenous leukemia resembled malignant tissue in their metabolism; immature cells from cases of myelogenous leukemia, and both mature

29. Bakker (footnote 8, first reference).

30. Murphy, J. B., and Hawkins, J. A.: Comparative Studies on the Metabolism of Normal and Malignant Cells, J. General Physiol. **8**:115, 1925.

31. Hawkins, J. A.: A Discussion of Recent Studies on the Metabolism of Normal and Malignant Cells, J. General Physiol. **9**:771, 1926; footnote 13, second reference.

and immature cells from cases of lymphatic leukemia resembled embryonic tissue.

Such comparisons are of value chiefly to bring out the fact that the metabolism of the white blood cells does differ in marked degree from that of most other normal tissues. That this difference may be of considerable physiologic importance is indicated by the work of Fleischmann,[32] who showed that when cell respiration is fully inhibited by 0.005 molar hydrocyanic acid, phagocytosis and ameboid motion of leukocytes from blood as well as from peritoneal exudate are fully retained, the necessary energy being derived from glycolysis. It is suggested by Bakker and by Fleischmann that this "anoxybiotic" activity of the leukocytes may be of importance in enabling them to live and function in exudates, where the supply of oxygen is slight. Okamoto [33] has shown that malignant tissue likewise can live for several days without oxygen. While knowledge of the differences in the metabolic activity of these various types of cells is at present of chiefly theoretical interest, it is to be hoped that it may ultimately prove to be of some practical value in the understanding and treatment of disease.

SUMMARY

1. The metabolism of the white blood cells of leukemic blood varies according to the degree of maturity of the cells.

2. The oxygen consumption is greater, the more mature the cells, whereas the sugar consumption (glycolysis) tends to be smaller, the more mature the cells.

3. When calculated on the basis of weight, the rate of sugar consumption of lymphatic white blood cells does not differ from that of myelogenous cells of approximately the same degree of maturity.

4. The metabolism of normal white blood cells is similar to that of relatively mature cells from patients with leukemia, but more active, as regards both oxygen and sugar consumption.

5. Slight degrees of cell injury exert a marked effect on the rate of oxygen consumption, much less on the rate of sugar consumption.

6. When measured under aerobic and anaerobic conditions (in the presence of 95 per cent oxygen and 95 per cent nitrogen, respectively), the sugar consumption of normal white blood cells and mature myelogenous cells from leukemic blood resembles that of cancer tissue, whereas the sugar consumption of immature myelogenous cells and of both mature and immature lymphatic cells is of the type considered characteristic of embryonic tissue.

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32. Fleischmann, W.: Ueber Anoxybiose von Leucocyten, Biochem. Ztschr. **184**:385, 1927.

33. Okamoto, Y.: Ueber anaerobiose von Tumorgewebe, Biochem. Ztschr. **160**:52, 1925.

II. THE DIFFUSIBLE CALCIUM AND THE PROTEINS OF THE BLOOD SERUM IN MALIGNANT DISEASES *

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Several workers have suggested that abnormalities in calcium metabolism may be significant in the genesis and development of neoplasms in man and in other animals. Thus Clowes and Frisbie [1] found calcium to be markedly low and potassium high in actively growing malignant tissue. Goldzieher [2] and Theis and Benedict [3] reported low values for the total serum calcium in patients afflicted with carcinoma and other malignant tumors. Reymond, Sendrail and Lassalle [4] and Sendrail [5] claimed that a lowering of the serum calcium occurred in the precancerous phase of animals with experimentally induced neoplasms. Finally, McDonald [6] went so far as to state that cancer is a disease associated with a lessened amount of total and ionized calcium in the blood. These observations led us to investigate the calcium fractions, the proteins and

* Submitted for publication, Nov. 30, 1929.

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* This research is one of a series carried out jointly in the Department of Medicine and the Division of Biochemistry of the University of California Medical School, with the cooperation of Professors W. J. Kerr and Carl L. A. Schmidt.

1. Clowes, G. H. A., and Frisbie, W. S.: On the Relationship Between the Rate of Growth, Age, and Potassium and Calcium Content of Mouse Tumors (Adeno-Carcinoma, Jensen), Am. J. Physiol. **14**:173, 1905.

2. Goldzieher, M.: Experimentelle Beiträge zur Biologie der Geschwüdste, Verhandl. d. deutsch. Gesellsch. f. Chir. **15**:283, 1912.

3. Theis, R. C., and Benedict, S. R.: Inorganic Constituents of the Serum in Cancer, J. Cancer Research **8**:499, 1924.

4. Reymond, A.; Sendrail, M., and Lassalle, C. A.: Variation of Ion Balance in Experimental Cancer, Compt. rend. Soc. de biol. **93**:1061, 1925.

5. Sendrail, M.: The Precancerous Phase, Néoplasmes **5**:99, 1926.

6. McDonald, Ellice: A Theory of Cancer Causation with Some Unfinished Results, M. J. & Rec. **125**:795 (June 15) 1927; abstr., J. A. M. A. **89**:824 (Sept. 3) 1927.

the inorganic phosphate of the blood serum in fifteen patients suffering from malignant diseases.

Recent work in the field of calcium metabolism [7] has shown that a measurement of the diffusible fraction of the serum calcium is a measure of the physiologically available calcium as demonstrated by its decrease in tetany,[8] and by its increase after the administration of adequate doses of parathyroid extract,[9] or after the ingestion of calcium salts.[10]

By the diffusible calcium is meant that portion of the serum calcium which will diffuse through a collodion membrane completely permeable to crystalloids. Experimental work has shown that the diffusible calcium fraction of the blood serum is not entirely ionized, but that it does contain essentially the same concentration of ionic calcium as in the blood.[11] As opposed to the diffusible calcium, the nondiffusible calcium is that fraction of the serum calcium held back by a collodion membrane

7. Stewart, C. P., and Percival, G. H.: Calcium Metabolism, Physiol. Rev. **8**:283, 1928.

8. Von Meysenbug, L., and McCann, G. F.: The Diffusible Calcium of the Blood Serum: II. Human Rickets, and Experimental Dog Tetany, J. Biol. Chem. **47**:541, 1921. Liu, S. H.: A Comparative Study of the Effects of Various Treatments on the Calcium and Phosphorus Metabolism in Tetany; Chronic Juvenile Tetany, J. Clin. Investigation **5**:259, 1928.

9. Data accumulated by the authors have not been published. Recently Cantarow (Arch. Int. Med. **44**:834 [Dec.] 1929), in order to avoid the theoretical drawbacks attending the direct analysis of the diffusible calcium of the serum as obtained by the combined method of ultrafiltration and diffusion, measured the spinal fluid calcium at intervals after the injection of parathormone. He assumed that the spinal fluid calcium represented at all times a measurement of the diffusible calcium of the blood. Cantarow found that the rise in the total calcium of the blood was not followed by a parallel rise in the spinal fluid and concluded thereby that it was the nondiffusible calcium fraction that increased after the injection of parathyroid hormone. His observations are in direct contradiction to those of other workers who determined the fractions of the serum calcium by direct analysis after separation through a collodion membrane. Unless it can be shown that the rate of change in the spinal fluid calcium and the magnitude of the change are identical with those in the blood stream at any given moment, while marked fluctuations are taking place in the blood stream, Cantarow's analyses of the spinal fluid must be interpreted with considerable caution in their application to the state of the diffusible calcium of the serum. In a recent communication (J. Biol. Chem. **85**:491 [Jan.] 1930) we discussed the theoretical objections to the direct analysis after diffusion and ultrafiltration and offered a simplified method for the direct examination of the diffusible calcium of the serum after ultrafiltration through a collodion membrane.

10. Moritz, A. R.: The State of the Serum Calcium in Experimental Hypo and Hypercalcemia, J. Biol. Chem. **66**:343, 1925.

11. Neuhausen, B. A., and Pincus, J. B.: A Study of Several Inorganic Constituents of Serum by Ultra Filtration, J. Biol. Chem. **57**:99 (Aug.) 1923. Stewart, C. P., and Percival, G. H.: Calcium in Corpuscles, Plasma and Serum, Biochem. J. **22**:548, 1928.

completely permeable to crystalloids. Loeb and Nichols [12] and Greenberg [13] have shown this fraction to be bound to the proteins in the form of a calcium-protein complex ion. From this, it is to be expected that the amount of the nondiffusible calcium of the serum will depend primarily on the amount of the serum proteins present.[14]

Theoretically, the determination of the ionic calcium would be the ideal manner of evaluating the availability of calcium for physiologic purposes. But lacking methods of clinical practicability for such measurements, we must depend, qualitatively at least, on alterations in the diffusible calcium which contains the ionic fraction, to indicate the state of the available calcium. That this is of practical value has been demonstrated by Liu [15] in chronic tetany, and by us in parathyroid tetany.[16] In these diseases, in which a known deficiency in serum calcium exists, it is the decrease in the diffusible fraction of the calcium that was found to be important. If significant alterations in the functional activity of the blood calcium exist in carcinoma or in other malignant diseases, it might be expected that the values for the diffusible fraction of the blood serum calcium would show these changes.

EXPERIMENTAL WORK

The total calcium was determined by Tisdall's modification of the Kramer-Tisdall method.[17] The diffusible calcium was estimated by ultrafiltration of the blood serum through a specially prepared collodion membrane, and the nondiffusible calcium was obtained by difference between the total and the diffusible calcium.[14] The inorganic phosphate was determined by Fiske and Subbarow's method.[18] The serum proteins were estimated according to the colorimetric method described by one of us.[19] A more complete description of the experimental procedure is to be found in a communication especially devoted to this subject.[14]

12. Loeb, R. F., and Nichols, E. C.: Factors Influencing the Diffusibility of Calcium in Human Blood, J. Biol. Chem. **72**:690, 1927.

13. Greenberg, D. M.: Electrical Transference of Calcium in Blood Serum Protein Solutions, J. Biol. Chem. **79**:177, 1928.

14. Greenberg, D. M., and Gunther, L.: On the Determination of the Diffusible and Nondiffusible Serum Calcium, J. Biol. Chem. **85**:491 (Jan.) 1930.

15. Liu (footnote 8, second reference).

16. The diffusible calcium in parathyroid tetany will be the subject of another communication.

17. Tisdall, F. F.: A Note on the Kramer-Tisdall Method for the Determination of Calcium in Small Amounts of Serum, J. Biol. Chem. **56**:439, 1923.

18. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

19. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, J. Biol. Chem. **83**:545, 1929.

RESULTS

The analytic results are shown in the accompanying table. Seven of the fifteen patients exhibited values for the total serum calcium definitely below the normal limits in conformity with the observations of Goldzieher [2] and Theis and Benedict,[3] which they set at from 9.3 to 10.5 mg. per hundred cubic centimeters.[20]

Analytic Data

Patient	Calcium			Inorganic Serum Phosphorus, Mg. per 100 Cc.	Serum Proteins in per Cent		Comment
	Total Serum, Mg. per 100 Cc.	Diffusible, Mg. per 100 Cc.	Nondiffusible, Mg. per 100 Cc.		Albumin	Globulin	
Swa.....	10.5	5.2	5.3	2.6	4.0	1.6	Endothelial myeloma of humerus
Col.....	9.8	5.7	4.1	3.3	5.1	2.4	Carcinoma of lung
San* (1)..	7.6	4.8	2.8	3.6	4.0	2.6	Carcinoma of pylorus
(2)..	7.5	4.7	2.8	3.7	4.0	2.4	
(3)..	7.2	Lost	...	...	4.2	2.3	(Plasma CO_2 = 73 per cent by volume)
Kls.....	8.1	4.0	4.1	3.1	3.6	2.8	Generalized carcinomatosis
Ysu.....	9.0	4.2	4.8	3.7	4.1	2.1	Carcinoma of sigmoid colon
Ros.....	9.3	4.4	4.9	3.7	4.4	3.6	Hemangioma of pleura
Zel.....	9.5	5.3	4.2	3.8	3.9	2.8	Hodgkin's disease
Dun.....	9.9	4.8	5.1	3.1	5.1	2.4	Carcinoma of tongue
Ash.....	9.3	4.5	4.8	3.3	4.1	2.5	Inoperable cancer of the stomach
Pat.....	9.9	4.8	5.1	3.8	4.8	2.7	Cancer of the small intestine
Fra †.....	7.7	5.1	2.6	2.9	3.6	2.6	Carcinoma of ampulla of Vater
Swe †.....	8.6	4.5	4.1	3.5	4.2	2.5	Carcinoma of head of pancreas
Bles †....	8.1	4.5	...	...	...	...	Primary carcinoma of cecum, secondary of liver
Mar †....	9.2	6.4	...	...	...	...	Carcinoma of head of pancreas
Bob †....	10.0	5.4	...	...	...	...	Carcinoma of common bile duct

* Sample 1 was drawn Nov. 5, 1928; sample 2, Dec. 6, 1928, and sample 3, Dec. 10, 1928.
† Patients were jaundiced. The presence of jaundice has been shown by us not to alter the diffusible calcium (footnote 16).

In marked contrast to the values for the total calcium, four being definitely below 8.5 mg. per hundred cubic centimeters, it is seen that all but one of the values for the diffusible calcium are above the lowermost limit of 4.2 mg. per hundred cubic centimeters. For the patients on whom the serum proteins were determined, it is to be noticed that there is a rough parallelism between the nondiffusible calcium fraction and the

20. In a more recent discussion, Criep and McElroy (Arch. Int. Med. **42**:865 [Dec.] 1928) placed these limits for the total serum calcium between 8.5 and 11.7 mg. per hundred cubic centimeters. We have found (this issue, page 72) the normal values for the diffusible calcium of the serum of adults to vary between 4.2 and 6.8 mg. per hundred cubic centimeters and those for the nondiffusible calcium to vary between 4.1 and 7.4 mg. per hundred cubic centimeters.

content of the serum proteins.[21] The fact that the fall of the serum proteins is concomitant with a qualitative fall in the nondiffusible calcium offers an explanation for the apparent deficiency of the blood calcium as seen in the total serum calcium values.

In six of the patients, jaundice of varying degrees was also present. We have shown in an earlier communication[22] that the presence of jaundice in no way alters the conclusions to be drawn from the analytic data. The inorganic serum phosphorus in all our cases showed no significant deviations from the usually accepted normal values.

Our observations indicate that the diffusible calcium is within the limits of normal variations in malignant diseases. If the diffusible calcium may be considered a measure of the physiologically available calcium, we may conclude that it is present in adequate amounts in malignant disease, and that the blood calcium is apparently not a factor in the etiology of such diseases.

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21. The only striking exception to this seems to be patient San. Since we were able to run three sets of analyses on blood drawn at intervals over a period of more than a month, the analytic observations cannot be doubted. This case was also complicated by having a considerable alkalosis as shown by the plasma carbon dioxide content of 73 per cent by volume.

22. Gunther, L., and Greenberg, D. M.: I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930.

III. THE DIFFUSIBLE CALCIUM OF THE BLOOD SERUM IN ALLERGIC DISEASES*

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The calcium metabolism in allergic diseases has recently been the subject of investigation by a number of workers. The principal method of approach has been through the study of the total calcium content of the serum by methods similar to the Kramer and Tisdall method [1] for the analysis of the blood for calcium. Such studies have been based mostly on the assumption of a deficiency of calcium in the blood and are supported principally by the indirect evidence that symptomatic relief has been obtained in certain instances through therapy with calcium salts. The mass of the analytic data, however, critically reviewed, indicates that the total serum calcium values lie within the range of normal variation.[2] For a discussion of the normal values, the reader is referred to the recent work of Criep and McElroy,[2] who also reviewed the present status of calcium therapy in atopy.

As a part of the general problem in the study of the diffusible calcium of the blood serum in a number of pathologic conditions undertaken in this laboratory, fourteen cases of various allergic conditions were studied. Patients who were suffering from asthma of bacterial and specific protein origin, hay-fever, eczema, and urticaria caused by a specific protein and dermatographia were included.

The specimens of venous blood were for the most part obtained during fasting, in the morning. Work done in our laboratory indicates

* Submitted for publication, Nov. 30, 1929.

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* This research is one of a series carried out jointly by the Division of Biochemistry and the Department of Medicine of the University of California Medical School with the cooperation of Professor William J. Kerr and Professor Carl L. A. Schmidt.

1. Kramer, B., and Tisdall, F. F.: Distribution of Sodium, Potassium, Calcium and Magnesium Between Corpuscles and Serum of Human Blood, J. Biol. Chem. **53**:241, 1922.

2. Criep, L. H., and McElroy, W. S.: Atopy, Arch. Int. Med. **42**:865 (Dec.) 1928.

that a blood specimen taken during fasting is not essential.[3] The diffusible calcium was obtained by ultrafiltration of the blood serum through a collodion membrane by the method of Greenberg and Gunther.[4] The normal concentration of the diffusible calcium of the blood serum in adults, we have found,[5] varies in the main between 4.5 and 6 mg. per hundred cubic centimeters of serum, with extreme ranges between 4.2 and 6.8 mg. per hundred cubic centimeters and an average value of 4.96 mg. per hundred cubic centimeters. For the diffusible calcium of the blood serum of normal children, to our knowledge, no figures are as yet available.

The results are tabulated in the accompanying table. The series is not large enough for detailed statistical analysis, but indicates the general

Results of Analyses of the Blood Serum of Allergic Patients for Calcium

Patient	Age, Years	Total Calcium, Mg. per 100 Cc.	Diffusible Calcium, Mg. per 100 Cc. of Ultrafiltrate	Remarks
De*	14	9.9	4.8	Hay-fever, eczema
Ne*	11	10.2	4.4	Asthma
To*	12	9.0	4.3	Asthma, eczema, hay-fever
Ku*	9	....	4.0	Asthma
Do*	8	9.2	5.0	Asthma, hay-fever
Sh*	..	....	4.3	Asthma
Sha*	..	10.1	5.2	Asthma
Ne	Adult	10.3	5.3	Hay-fever, eczema
Fo	Adult	11.2	5.3	Dermatographia
Lu†	Adult	9.6	5.2	Asthma
Ku†	Adult	9.8	5.1	Asthma
Li†	Adult	10.3	5.6	Asthma
Bu†	Adult	10.1	5.2	Asthma
Ca	Adult	11.0	5.3	Dermatographia

* Blood samples were obtained through the courtesy of Dr. George Piness and Dr. Hyman Miller, Los Angeles, from their allergic service at the Children's Hospital, Hollywood, Calif.
† Blood samples were obtained through the courtesy of Dr. Albert H. Rowe, Oakland, Calif.

trend of the diffusible calcium in the allergic diseases enumerated. The analyses show that the calcium values lie within the normal range of variation, the only significant exception being the value in the case of Ku. The figures for the children's cases in the table tend to be somewhat lower than those for the adults. That the values for diffusible calcium lie within the normal range of variation in eczema, hay-fever, urticaria, etc., is a particularly significant observation, for the diffusible calcium of the

3. Unpublished data taken by the authors on experiments with the ingestion of calcium.

4. Greenberg, D. M., and Gunther, L.: On the Determination of Diffusible and Non-Diffusible Serum Calcium, J. Biol. Chem. **85**:491, 1930.

5. Gunther, L., and Greenberg, D. M.: I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930.

serum is, to all purposes, physiologically available calcium.[6] It is this fraction of the serum calcium that contains the same concentration of ionic calcium as in the blood, although the ultrafiltrable calcium is not all ionized.[7]

Our analyses of the serum in allergic diseases show values for the diffusible and nondiffusible calcium (obtained by subtraction of the value of the diffusible calcium from that of the total calcium[8]) that vary together within the normal range; but this is so only because the diffusible calcium is normal. Data from our experiments[9] indicate that except in diseases in which there is a marked reduction in serum proteins (which causes an abnormal degree of variation in the nondiffusible calcium), physiologic variations in the calcium occur ordinarily in the diffusible calcium fraction, often with little concomitant variation in the total calcium values. This has been shown in a striking manner in the tetany of parathyroid deficiency by ourselves,[10] which also confirms the work of Liu.[11] In view of these facts, the observation that the total and diffusible fraction of the blood serum calcium vary together within the normal range in allergic diseases indicates that physiologically available calcium is present in the blood in adequate amounts.

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6. Stewart, C. P., and Percival, G. H.: Calcium Metabolism, Physiol. Rev. **8**:283, 1928; Calcium in Corpuscles, Plasma and Serum, Biochem. J. **22**:548, 1928. Moritz, A. R.: The State of the Serum Calcium in Experimental Hypo and Hypercalcemia, J. Biol. Chem. **66**:343, 1925.

7. Stewart and Percival (footnote 6). Neuhausen, B. S., and Pincus, J. B.: A Study of the Condition of Several Inorganic Constituents of Serum by Means of Ultrafiltration, J. Biol. Chem. **57**:99 (Aug.) 1923.

8. Greenberg and Gunther (footnotes 4 and 5).

9. Gunther and Greenberg (footnote 5); II. Studies on the Diffusible Calcium and the Proteins of the Blood Serum in Carcinoma and Other Malignant Diseases, this issue, p. 67.

10. The tetany of parathyroid deficiency will be the subject of another communication.

11. Liu, S. H.: A Comparative Study of the Effects of Various Treatments on the Calcium and Phosphorus Metabolism in Tetany; Chronic Juvenile Tetany, J. Clin. Investigation **5**:259, 1928.

SO-CALLED MALIGNANT HYPERTENSION

A CLINICAL AND MORPHOLOGIC STUDY *

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Recent work in America and abroad has emphasized the importance of a group of rapidly fatal cases associated with excessive hypertension. Among the various terms that have been employed to define this condition those most commonly used are "malignant hypertension," "malignant renal sclerosis of Fahr," "genuine contracted kidney" and "chronic interstitial nephritis."

The term "malignant hypertension" was first used by Volhard and Fahr [1] to designate cases of renal arteriosclerosis in which renal failure later developed. They assumed that the condition was caused by the addition of an inflammatory process to a kidney already damaged by arteriosclerosis, leading to infarction and necrosis of the glomerular loops. Fahr [2] later introduced the anatomic expression "malignant renal sclerosis" to designate changes in the kidney characterized by necrosis of the afferent glomerular arterioles and the capillary loops, with inflammatory changes in the corresponding glomerulus.

Keith, Wagener and Kernohan [3] employed the term "malignant hypertension" in a slightly different sense. They applied it to a clinical condition with the following characteristics: persistent hypertension with a progressively downward course, moderate or no renal failure, absence of anemia, cardiac hypertrophy and distinctive changes in the retina. Anatomically, they emphasized the widespread involvement of the arterioles of the entire body.

Since there has been considerable difference of opinion concerning the essential nature of this class of cases, the present investigation was undertaken in an attempt to contribute to the correlation of the clinical observations and the corresponding morphologic changes in the arterial

* Submitted for publication, Dec. 3, 1929.

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1. Volhard, F., and Fahr, T.: Die Brightische Nierenkrankheit, Klinik Pathologie und Atlas, Berlin, Julius Springer, 1914.

2. Fahr, T.: Ueber Nephrosclerose, Virchows Arch. f. path. Anat. **226**:119, 1919.

3. Keith, Norman M.; Wagener, Henry P., and Kernohan, James W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928.

Summary of Clinical Data

Case	Age, Years	Date	Blood Pressure		Blood Chemistry			Renal Function Tests				Urinalysis			Red Blood Cells	Chief Complaint	Duration of Illness Prior to This Study
			Systolic	Diastolic	Non-protein Nitrogen	Creatinine	Cholesterol	Phthalein, per Cent per 2 Hours	Concentration Test: Highest Specific Gravity	Concentration Test: Lowest Specific Gravity	Urea Concentration Factor McLean	Albumin	Doubly Refracting Lipoids	Microscopic Observations			
1	34	2/18/28	210	115	44	2.4	178	35	1.018	1.005	..	0	0	Negative	3,500,000	Headache	4 years
	34	4/13/28	180	100	38	1.8	...	40	1.020	1.006	..	0	0	Negative	.....	Headache	
	34	7/17/28	240	160	104	4.2	160	10	1.009	1.004	15	+++	0	Many red blood cells; few white blood cells; no casts	2,050,000	Headache and abdominal cramps	
2	42	8/22/28	255	160	35	1.4	255	40	1.018	1.008	38	0	0	Negative	4,040,000	Headache and loss of weight	8 years
	42	1/30/29	200	170	49	2.0	178	25	1.023	1.010	30	0	0	Negative	.....	Headache and dyspnea	
3	37	3/28/24	215	125	38	1.5	...	75	1.024	1.004	..	0	...	Negative	5,400,000	Dizziness and loss of strength	7 months
	41	6/ 3/28	280	150	34	1.9	...	60	1.025	1.010	..	++	...	Few red blood cells; pus cells and casts	4,000,000	Headache; loss of weight and strength	
	41	3/12/28	290	160	51	2.2	166	30	1.015	1.009	..	+++	...	Many red blood cells; pus cells and granular casts	3,140,000		
4	57	12/ 2/26	240	150	52	2.9	104	10	1.010	1.006	20	+	0	Few red blood cells and granular casts	3,310,000	Headache and loss of weight	1 year
	57	1/ 4/27	220	150	76	2.8	109	15	1.015	1.005	..	++	0	Few red blood cells and granu-	.....	Headache and loss of weight	
5	53	11/ 7/26	210	115	48	3.2	150	25	1.008	1.004	..	+++	0	Many red blood cells and granular casts	4,500,000	Headache, dyspnea and weakness	3 months
		1/15/27	245	150	120	8.0	142	5	1.011	1.007	..	+++	0	Many red blood cells and granular casts	.....	Headache and emaciation	5 months
6	52	7/29/25	230	125	42	...	154	15	1.020	1.005	60	+++	0	Few red blood cells; pus cells and casts	4,000,000	Headache	1 month
	53	11/16/26	180	110	36	...	210	15	.....	.....	45	+	0	.....	.....	Headache	
7	32	12/21/26	205	130	40	2.0	265	70	1.024	1.010	52	++	0	Negative	4,080,000	Headache and left-sided paralysis	9 years

	33	3/17/27	190	135	29	2.3	...	25	1.020	1.015	20	Trace	c	Negative	.....	Headache and left-sided paralysis	
	33	5/31/27	160	130	23	1.9	277	30	1.016	1.009	25	Trace	0	Negative	.....	Headache	
8	17	11/30/27	270	155	57	2.8	...	70	1.025	1.010	..	++	0	Many red blood cells	4,500,000	Headache and visual disturbance	5 months
	17	2/16/28	280	160	96	3.0	145	65	1.015	1.005	..	++++	0	Many red blood cells	.....	Headache and abdominal cramps	
	18	5/20/28	260	135	85	2.5	165	60	1.014	1.006	..	++++	0	Many red blood cells	2,750,000	Headache and abdominal cramps	
9	9	9/ 3/27	205	155	29	2.0	...	45	1.018	1.006	..	Trace	0	Negative	4,980,000	Headache	1 year
	10	4/14/28	132	100	35	1.5	...	40	1.015	1.005	..	0	0	Negative	3,600,000	Headache	
	10	10/11/28	240	150	45	8.6	...	30	1.020	1.005	..	++	0	Many red blood cells	3,420,000	Headache, convulsions and bloody urine	
	11	4/18/29	208	180	99	3.2	...	25	1.020	1.008	..	+++	0	Many granular casts; few red blood cells	3,690,000	Headache, dyspnea and edema	
10	56	11/12/28	240	140	46	3.0	164	10	1.014	1.009	33	++	0	.....	3,700,000	Headache and dyspnea	5 years
	56	5/13/29	220	142	145	10.0	192	0	1.012	1.006	..	+++	0	Many red blood cells	.....	Headache	
11	42	12/28/28	222	132	40	1.8	236	15	1.012	1.004	..	+++	0	Many red blood cells	3,670,000	Headache	8 months
		1/ 7/29	190	105	30	2.6	206	5	1.015	1.010	..	+++	0	Many red blood cells	.....	Headache	
12	50	3/13/29	220	115	80	3.0	210	25	1.018	1.009	28	++++	0	Many red blood cells; pus cells and granular casts	4,150,000	Headache and weakness	1 year
13	24	7/26/27	234	178	22	1.5	195	65	1.023	1.012	37.2	+	0	Few red blood cells and granular casts	3,780,000	Headache, loss of weight and weakness	1 month
	24	12/ 2/27	285	160	154	5.8	140	0	1.014	1.009	12	++++	0	Many red blood cells and granular casts	3,130,000	Headache and weakness	
14	..	2/ 2/29	230	120	32	1.6	152	15	1.016	1.010	18	+++	0	Few granular casts, red blood cells and pus cells	4,000,000	Headache and nocturia	5 months
	47	6/ 4/29	238	140	30	1.3	178	30	1.012	1.004	22	+++	0	Few granular casts, red blood cells and pus cells	.....	Headache	
15	38	3/12/29	250	140	24	1.8	155	45	1.022	1.012	32	++	0	.....	3,050,000	Headache and dyspnea	1 year
		6/ 1/29	280	160	48	2.9	140	25	1.018	1.009	18	++++	0	.....	3,280,000	Headache	
16	19	7/ 5/25	275	150	18	1.4	170	65	1.025	1.005	..	0	0	.....	4,180,000	Headache	6 months

system of the body. For the purpose of this study, sixteen cases were selected from a total of 629 cases studied between Jan. 1, 1925 and July 1, 1929. This total group included all cases in which the diagnosis was chronic nephritis, arteriosclerosis with hypertension or essential hypertension. Cases of decrescent or senile arteriosclerosis were omitted from the study. Of the sixteen patients, thirteen died; on twelve, autopsy was done. In the clinical study, attention was directed especially to the hypertension and renal function, the condition of the heart and the larger peripheral arteries, and cerebral and retinal changes. Histologically, smaller arteries and arterioles were especially studied in the kidney, liver, pancreas, spleen, heart and skeletal muscle; we were rarely permitted to examine the brain.

ANALYSIS OF THE CLINICAL DATA

There was a wide variation in the clinical manifestations of the patients, depending on the development of heart failure, renal failure, cerebral hemorrhage and the rate of progress of the disease. Six patients died of renal failure, three of heart failure, two of apoplexy and one of a ruptured dissecting aneurysm on the basis of an atherosclerotic ulcer in the aorta. Some patients, for example the one in case 2, developed both renal failure and heart failure toward the close of the illness.

The ages of the patients in this series ranged from 9 to 57 years. Eight patients were above 40 and eight were under 40 years of age. Three were above 50, while three were less than 19 years of age. The sex and age of the patients appeared to have no influence on the severity of the symptoms and the rapid progress of the disease. A systolic blood pressure of 250 or above and a diastolic pressure of 150 or above were not unusual observations. The interval that elapsed between the onset of hypertension and the occurrence of symptoms referable to hypertension was not known in all cases, although in case 2 it was at least eight years. In other cases an interval of from two to five years was known to have elapsed. It is known that in case 3 the blood pressure was normal eight months before the onset of symptoms. Aside from the height of the blood pressure, it was observed that the hypertension of this group did not show the fluctuation seen in the early stages of the so-called "benign" group. Blood pressure reducing substances brought about a fall in pressure in cases 8 and 9, but there was no alleviation of the chief symptoms. On discontinuing the treatment, the blood pressure promptly rose to its former high level. In no case was there a definite remission in the hypertension as is often seen in the early benign form, but the hypertension persisted from the onset until the end.

Renal function was carefully studied in all the cases reported here. The laboratory data in connection with tests of kidney function are given in the table. Renal failure with uremia developed in six cases. Convulsive seizures occurred only in case 2. Albuminuria was present in all the cases during the later periods of the disease. It was difficult to determine accurately in most instances just how long albuminuria had existed before the last illness, although in most cases it is certain that albuminuria developed late in the disease. Undoubtedly there was considerable variability in the period of time elapsing between the onset of the hypertension and the onset of albuminuria. In some patients albuminuria developed early in the course, and in others later on, probably depending on the severity of changes in the vessels of the kidney. A striking feature of the urinary picture was hemorrhage from the kidneys in cases 1 and 8. In case 1 the hemorrhage could be accounted for at autopsy from the necrosis of the arterioles and glomerular loops, but in case 8 no necrotic areas were found.

Palpation of the peripheral arteries, such as the radials, temporals and brachials, disclosed no constant gross changes. It was found that in general the patients above 40 years of age had tortuous arteries the walls of which were hardened, and that those under 40 had wiry, straight arteries which were under tension but the walls of which could not be called hardened. Some arteries were calcified, such as those described in case 5. No doubt there are numerous other factors, not under consideration here, which contributed to the tortuosity and thickness of the peripheral arteries.

With regard to the condition of the heart in the cases studied, there were wide variations. Cardiac hypertrophy was present in every case, although more pronounced in some than in others. Despite the great increase in the size of the heart in some of the patients, circulation was unimpaired and death came through other channels. Heart failure caused death in three of the cases. Pulmonary edema and profound dyspnea, usually worse at night (cardiac asthma), were the chief clinical manifestations. In most cases, the liver was enlarged and firm; in the cases of heart failure, it was engorged and tender. Cyanosis and Cheyne-Stokes' respiration, with moderate edema and ascites, were clinical features of patients who died of heart failure.

The Wassermann reaction of the blood was positive, four plus, in two cases; in case 8 it was negative, although both the father and the mother had syphilis. It does not appear, then, that syphilis is an essential factor in exciting malignant hypertension.

Abdominal cramps simulating gallstone colic were frequently present, though not constantly so, in cases 1 and 8. Definite anemia was found in eight of the sixteen cases studied; it was moderate in all these cases except 1 and 8 in which it was severe. In the early periods

of the disease, anemia was usually not present, but developed in the later stages and especially in those cases characterized by renal failure. An outstanding symptom in all cases was headache; it was the first symptom complained of in most cases, and often made life almost unbearable for the sufferer. These symptoms in conjunction with the ophthalmoscopic observations in some cases suggested a diagnosis of tumor of the brain. Marked weakness and loss of weight were present in all cases; frequently these developed to a pronounced degree before signs of renal failure, heart failure or cerebral hemorrhage occurred.

From the ophthalmologic standpoint, all cases showed either a choked disk or retinal edema accompanied by hemorrhages. The arteries were narrowed, and in some cases straight, in others tortuous. The retinal changes were indicative of various degrees of neuroretinitis. Hemorrhages from the nose, the stomach and the intestinal tract were found in case 8. Nausea and vomiting were present in all cases.

The clinical features in the cases described here differed from those in essential or benign hypertension. The chief dissimilarity consisted in the greater severity of symptoms and the rapid functional breakdown of the involved organs in the malignant type. That there should be variation in the clinical observations is expected from the nature of the disease. Essentially, the malignant type is a widespread disorder of the arterial system of the body, involving many or all bodily structures and leading at times to a more profound impairment of one organ than of another. Furthermore, some organs and structures of the body may be severely affected by this vascular disease without any functional disturbance being felt by the patient. This is exemplified by the extensive vascular changes seen in the spleen in all cases. In most of the cases presented here, the hypertension syndrome existing prior to the onset of the last illness had the qualities of a benign hypertension. The forces responsible for the conversion of the benign into the malignant form are not known.

ANALYSIS OF PATHOLOGIC DATA

All sections were studied with hematoxylin and eosin, van Gieson's and Weigert's elastic tissue stains and sudan III. Polariscopic examinations were done when fat was found. The outside diameter of many of the smallest arteries and arterioles was measured with a micrometer. The smallest arteries and arterioles were found to measure from 40 to 120 microns. Postmortem examinations were made in cases 1 to 12 inclusive. There was considerable dissimilarity in the morphologic changes in the organs and blood vessels, both grossly and microscopically. The heart was always found to be hypertrophied and there usually was arteriosclerosis of the larger branches of the coronaries. The walls of the smaller branches were thin and appeared fairly normal.

The size and the appearance of the kidneys were decidedly variable. Some kidneys were small, granular and contracted; others were larger than normal and smooth, and resembled those in subacute glomerular nephritis. In case 1, the kidneys had the appearance of those in embolic focal glomerular nephritis. Some kidneys were whitish and others were reddish. On microscopic examination, the smallest arteries and arterioles of the kidney as well as of the spleen, pancreas, liver and brain were almost universally involved in an arteriosclerotic process. The diffuse intimal thickening, causing a narrowing of the lumina, was characterized in some cases more by hyperplastic elastic thickening with proliferation of intimal connective tissue, and in others more by fatty and hyaline degeneration. Both processes were often combined in the same kidney. A striking feature was the hypertrophy of the media in some of the arterioles and smallest arteries of the kidney and other organs. In cases 2, 3, 4, 8, 9 and 11, in which these medial changes were distinct and conspicuous, there were also arteriosclerotic changes either of the same vessel or of some vessel in an adjoining area. Although many of the smallest arteries and arterioles in these cases showed hypertrophy of the media, the arteriosclerotic changes with reduction of the media were the outstanding features. In cases 5 and 7, although no medial hypertrophy was found in the renal vessels, it was present in the arterioles of the liver and spleen. In cases 1 to 7 inclusive, there were necrotic lesions in the walls of the afferent arterioles and many capillary loops in the corresponding glomeruli. The changes in these seven cases corresponded to the descriptions of malignant renal sclerosis of Fahr. In many tufts there was an increase of the endothelial cells of the capillary loops with a cellular exudate; in a few, epithelial crescents were found in Bowman's capsular space. Occasionally areas of lymphocytic infiltration and fibrosis were observed, replacing the renal functional tissue. The adventitia of the smallest arteries and arterioles was often found to be thickened. Periarterial lymphocytic infiltration was present in the interstitial connective tissue surrounding some of the smallest arteries and arterioles. Usually the adventitia did not participate in this reaction. In case 3, erythrocytes were seen to be infiltrating the necrosed arteriolar wall. In addition to the more acute and destructive lesions, an advanced arteriosclerotic process was seen, involving the smallest arteries and arterioles of the kidney.

The changes in the kidneys in cases 8 to 12 inclusive consisted of advanced arteriosclerosis of the smallest arteries and arterioles, leading in places to partial or complete obliteration of the lumina. No necrotic lesions were found in the glomerular loops. Some of the glomeruli showed fibrosis and hyalinization. Aside from the necrotic changes seen in the kidney in cases 1 to 7, the microscopic lesions in all cases

were essentially arteriosclerotic. None of the cases studied presented the histologic evidence characteristic of chronic glomerulonephritis. The smallest arteries and arterioles of the skeletal muscles of the body were studied in eight of the sixteen cases reported. In cases 2, 3, 8, 9, 10, 12 and 14, the media was found to be definitely thickened and there were no evidences of arteriosclerotic changes such as were found in the other organs of the body. No changes were found in case 11. No examination was made in the other cases. The smallest arteries and arterioles of the lungs appeared to be normal in all cases except one (case 9) in which there was hypertrophy of the media. Although advanced arteriosclerotic processes were seen in the vessels of the pancreas, spleen and liver, paralleling in severity those of the kidneys, no necrotic changes were found outside of the kidney. The microscopic changes in the vessels of the organs studied appeared to be manifestations of various degrees of an arteriosclerotic process.

Briefly, the changes in the smallest arteries and arterioles may be summarized as follows:

1. The lumina were almost universally narrowed and were sometimes obliterated by thickening of the vessel walls.

2. Hyperplastic elastic thickening of the intima was found, with proliferation of the connective tissue of the intima.

3. Fatty and hyaline degeneration involving the intima, and frequently the media, was prominent.

4. Medial thickening, consisting of hypertrophy of the muscular tissue, frequently occurred alone or in association with degenerative lesions of the intima.

5. Degenerative and proliferative lesions in the intima were usually accompanied by medial atrophy.

6. Occasionally there was periarterial lymphocytic infiltration of the interstitial connective tissue surrounding the smallest arteries and arterioles of the kidney.

7. Necrotic lesions were present in the walls of the arterioles and in the loops of the corresponding glomeruli in six cases.

8. Combinations of these changes were at times found involving the same vessel; in other cases the various lesions could be demonstrated side by side in the same histologic specimen.

9. The vessels of the skeletal muscles frequently showed thickening of the media, with normal intimal tissue.

10. The smallest arteries and arterioles of the lung were normal in all but one case.

COMMENT

Following the pioneer work of George Johnson [4] and of Gull and Sutton,[5] profound interest was aroused in a class of cases in which

4. Johnson, George: Lectures on Bright's Disease: With Especial Reference to Pathology, Diagnosis, and Treatment, London, 1873.

5. Gull, William; and Sutton, Henry: On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney (Arterio-Capillary Fibrosis), Tr. Medico-Chir. Soc. London **55**:273, 1872.

there were clinical hypertension, cardiac hypertrophy and termination with uremia, heart failure or apoplexy. Morphologically, a granular contracted kidney was found so commonly that the disease came to be called by names expressing the renal features. Of the many terms, those chiefly used were "red granular kidney," "contracted granular kidney" and "genuine Schrumphniere."

Although the lesions of the kidney were singled out for careful study, Gull and Sutton [5] suggested that many organs were diseased in this morbid condition and that the minute arteries in the kidney, spleen, brain, retina and skin were involved. It was also emphasized that the clinical picture might vary according to the structures chiefly affected, and that several or all organs might be affected simultaneously.

It was the opinion of George Johnson [4] that not only were the minute arteries in the kidney thickened, but the minute arteries of the skin and other parts of the body were similary changed; and he attributed the thickening to hypertrophy of their muscular tissue. He maintained that the kidneys were primarily at fault and incapable of secreting noxious agents, with the result that there developed a constriction of the arterioles of the body and subsequently a rise in the blood pressure and hypertrophy of the musculature of the smaller arteries and arterioles. Gull and Sutton believed differently, claiming that the vascular changes were independent of renal disease, and that the chief alterations consisted of a "hyaline-fibroid" formation, chiefly in the adventitia and intima, with atrophy of the muscular layer. They introduced the term "arteriocapillary fibrosis" for these changes.

Jores [6] who worked on the same problem with better methods, described the intimal thickening. He discovered that the intimal changes consisted of hyaline and fatty degeneration and elastic hyperplastic thickening of the intima. Such changes, according to Jores, led to narrowing of the lumen of the smaller arteries and arterioles. Jores failed to confirm Johnson's observation of medial muscle hypertrophy, and he agreed with Gull and Sutton that the vascular changes were widespread, leading at times to kidney disease and at other times to brain or heart failure with normal renal function. Jores found extensive degenerative changes in the intima of the arterioles of the brain, spleen, liver, pancreas and gastro-intestinal tract. In speaking of the media of the arteries and arterioles, he denied the existence of muscular thickening. He found the media reduced, and he emphasized again that the entire process was one of arteriosclerosis.

An examination of the case reports of the older writers shows conclusively that they encountered the class of cases described in recent

6. Jores, L.: Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, Virchows Arch. f. path. Anat. **178**:367, 1904.

years as malignant hypertension, although they did not attempt to differentiate the various types of vascular sclerosis. Gaskell,[7] however, separated the large class of primary vascular diseases into two groups. In the first subgroup he placed those characterized by a slow alteration of the kidney which was produced by what he called senile arteriosclerosis. In the second subgroup he found that the chief changes were due to a pronounced involvement of the arterioles and smallest arteries, and that they were distinguished clinically from the first class by a very high blood pressure, renal failure, cardiac hypertrophy and their occurrence in younger persons. Evans,[8] in describing the lesions of the smaller arteries and arterioles in diffuse hyperplastic sclerosis, stated that medial hypertrophy is a common observation, but that it is not the essential element nor a constant feature. The main feature in his opinion is an intimal thickening. The medial hypertrophy, he said, may be attributed to the hypertension.

The descriptive adjectives "benign" and "malignant," which were introduced by Volhard and Fahr,[1] aimed at separating renal arteriosclerosis into two distinct groups. The benign form included those cases in which the arteriosclerosis of the kidneys was not accompanied by renal insufficiency, while the malignant form included those in which there were inflammatory changes in the glomeruli and afferent arterioles in addition to the arteriosclerosis. This was the "combination form" or "bösartig" hypertension. Both authors later discarded the term "combination form." Volhard[9] introduced the theory that ischemia of the arterioles, dependent in part on vasoconstriction and in part on the swelling of the arteriolar walls, was the determining factor in the production of malignant hypertension.

According to Fahr,[10] the clinical differentiation between benign and malignant hypertension is readily accepted; but a unanimity of opinion concerning the pathogenesis of the two forms is difficult to obtain. Fahr expressed his belief that one is justified in speaking of two forms and not of two stages of renal sclerosis. He differentiated between the benign form and the malignant form of renal sclerosis. In the benign form, there is simple arteriosclerosis of the larger arteries and arterioles. There are fatty and hyaline degenerative changes in the afferent arterioles, with obliteration of many glomeruli. The tubules are normal, and

7. Gaskell, J. F.: On the Changes in the Glomeruli and Arteries in Inflammatory and Arteriosclerotic Kidney Disease, J. Path. & Bact. **16**:287, 1912.

8. Evans, Geoffrey: On the Nature of Arteriosclerosis, Brit. M. J. **1**:454, 1923.

9. Volhard, Franz: Die doppelseitigen hämatogenen Nierenerkrankungen (Bright'sche Krankheit), Berlin, Julius Springer, 1919, vol. 8, p. 576.

10. Fahr, T.: Ueber die Beziehungen von Arteriolensklerose, Hypertonie und Herzhypertrophie, Virchows Arch. f. path. Anat. **239**:41, 1922.

there is an increase of the interstitial connective tissue. Inflammation and necrotic changes are absent. Fahr compared this benign form with the arteriosclerotic contracted kidney described by Ziegler,[11] a condition affecting elderly people and distinguished histologically by arteriosclerosis of the larger and smaller arteries without renal failure. The malignant renal sclerosis of Fahr is distinguished from the benign form by the presence of inflammatory and necrotic changes in the arterioles and the glomeruli. In the tubular regions there are areas of round cell infiltration. Fahr expressed the opinion that malignant sclerosis may be a process restricted to the arterioles, but that at times larger arteries are involved. Extensive hyperplastic elastic intimal thickening of interlobular arteries may be present. A profound fatty and hyaline degeneration of the intima of the arterioles is found, with narrowing and occlusion of the lumen. In places there is extensive fatty degeneration of the entire arteriolar wall. Necrosis of the arteriolar wall is found, with infiltration by red blood cells. The glomeruli may be obliterated, partly collapsed or infarcted; other tufts may appear normal. There are cases in which the necrotic changes in the glomerular loops resemble embolic focal glomerular nephritis. In the larger renal arteries there is thickening of the media, with proliferative and degenerative changes in the intima.

That Fahr[12] found difficulty in separating sharply the benign from the malignant form is seen from his reports in which he described borderline cases or decompensated benign sclerosis. In this group there was no necrosis of the arterioles and glomerular loops, but there was a pronounced narrowing of the arterioles produced by arteriosclerosis, leading to a break-down of renal function.

Concerning the cause of malignant sclerosis, Fahr expressed the belief that vascular poisons affect the arterioles; some are unknown and some known. He assumed that the virus of rheumatic fever may at times be responsible for it. In his opinion, syphilis is an important factor in the pathogenesis of malignant sclerosis. The benign form of arteriosclerosis is due to wear and tear in a large sense. With respect to the involvement of the arterioles of the skin and skeletal muscles in malignant sclerosis, Fahr described various changes. Occasionally a mild arteriosclerotic process is found, with atrophy of the media. Usually he found these vessels normal. Sometimes the media is well developed in the arterioles and smaller arteries of the skin, the skeletal muscles and the intestinal tract. He stated that it is hard to decide

11. Ziegler, E.: Ueber die Ursachen der Nierenschrumpfung, Deutsches Arch. f. klin. Med. **25**:586, 1880.

12. Fahr, T.: Kurze Beiträge zur Frage der Nephrosklerose, Deutsches Arch. f. klin. Med. **134**:366, 1920.

whether an actual hypertrophy of the media exists because of the difficulty in judging the thickness of the wall. Fahr concluded that the arteriosclerotic changes are not caused by hypertension but that there are other forces causing the arteriosclerosis.

Arteriolonecrosis of the kidney was the term applied by Herxheimer [13] to a condition resembling Fahr's malignant sclerosis. He disagreed with Fahr's distinction between benign and malignant sclerosis, and maintained that they are terms applied to different stages of the same process and not to separate diseases. Herxheimer described cases of renal arteriosclerosis with uremia in which no changes corresponding to the malignant sclerosis of Fahr were found. Herxheimer attributed the chief lesions to rapidly developing arteriosclerotic changes in the arterioles in some cases, but he believed that these are the result only of the arteriolar sclerosis and not of an added inflammatory process. Many glomeruli have widened and ruptured loops, leading to hemorrhage into Bowman's capsular space. Grossly and microscopically, he stated, these kidney may resemble those of embolic focal glomerular nephritis seen in endocarditis lenta. Herxheimer described these arteriosclerotic lesions not only in the kidney but also in the liver, spleen, pancreas and brain, while he found other arterioles of the body free from changes.

Löhlein,[14] after investigating the arteriosclerotic contracted kidney, disagreed with Fahr that benign and malignant sclerosis were different in nature. He agreed with Jores, who also had studied this problem, and he concluded that there was no added inflammatory factor. It was emphasized by Löhlein that there was a difference in the size of the artery involved and in the extent of the arteriosclerotic process. In the benign form he found the arteries involved, with little glomerular disease, while in the malignant form the arterioles were universally diseased and glomeruli correspondingly involved. The arteriosclerotic process, however, was indentical in both cases, but in the malignant form there were advanced degenerative and proliferative changes which weakened the arteriolar wall in places, leading to dilatation. When such arteriosclerotic processes were severe enough, necrosis of the arteriolar and glomerular loops was present, and a histologic picture almost identical with glomerular nephritis was seen. Löhlein [15] did

13. Herxheimer, G.: Ueber Arteriolonekrose der Nieren, Virchows Arch. f. path. Anat. **251**:709, 1924.

14. Löhlein, M.: Ueber Schrumpfnieren, Beitr. z. allg. Path. u. path. Anat. **63**:570, 1917.

15. Löhlein, M., quoted by Kaufmann, E.: Pathology, Philadelphia, P. Blakiston's Son & Company, 1929.

not consider these changes indicative of an added inflammatory process. He summarized the glomerular changes as follows:

> Necrobiosis after collapse of all or portions of the loops subsequent to occlusion; then degeneration and atrophy with appearance of scars and remnants and débris of the Malpighian bodies; this is followed on the one hand, by reactive proliferative phenomena, degenerations, lipoid infiltration and cellular invasion, and on the other, by more or less retained structures in the loops. The changes remind us of chronic glomerulonephritis and are easily mistaken for inflammation.

Löhlein considered the glomerular changes similar to those in the arterioles; he stated that it was the tissue destruction which stimulated the reactive inflammatory processes, and that for this reason the latter were reparatory.

Löhlein found degenerative changes in the media of the larger arteries and arterioles of the kidney, but he did not mention that he found hypertrophy. He stressed the fact that in the malignant form the arteriolar lumen was narrowed in contrast to the benign form in which the lumen was wider than normal. The hypertension cannot be explained on the basis of arteriosclerosis, according to Löhlein.[16] The sclerosis is the effect of hypertension.

Hypertrophic changes in the media of all vascular structures of the body are described by Hueck [17] in his studies on arteriosclerosis. The elastic hyperplastic thickening of the intima, like medial hypertrophy of the arteries, is not classed as arteriosclerotic by Hueck but is an adaptation or functional phenomenon. Degenerative changes may follow these processes of adaptation, but not necessarily.

In his description of the "true arteriosclerotic contracted kidney," Kaufmann [18] mentioned a "second form," which developed suddenly, leading quickly to renal insufficiency, apoplexy or profuse hemorrhage. Anemia was a feature in contrast to the robust appearance of persons suffering from the usual form. The "second form" corresponds to malignant hypertension. Kaufmann expressed his belief that Fahr's benign and malignant types are only differences in degree of an arteriosclerotic process. He found no changes in the vessels of the body musculature.

In 420 cases of primary hypertension, Bell and Clawson [19] found thirty-six with definite renal insufficiency; twenty-seven of the thirty-

16. Löhlein, M.: Zur Nephrocirrhosis arteriosclerotica, Med. Klin. **14**:136, 1918.

17. Hueck, Werner: Anatomisches zur Frage nach Wesen und Ursache der Arteriosklerose, München. med. Wchnschr. **67**:535, 573 and 606, 1920.

18. Kaufmann, E.: Pathology, Philadelphia, P. Blakiston's Son & Company, 1929.

19. Bell, E. T., and Clawson, G. J.: Primary (Essential) Hypertension: A Study of Four Hundred and Twenty Cases, Arch. Path. **5**:939 (June) 1928.

six cases had a slowly progressive form of renal insufficiency ending eventually in uremia. Histologic examination of the kidneys in this group revealed a profound narrowing of the smaller arteries and arterioles, leading to a pure ischemic atrophy of the glomerular apparatus. Nine cases were characterized by uremia which came on rapidly. Histologically, necrosis of the arteries and arterioles was found, often with infarcted glomeruli. In four of the nine cases, acute inflammatory changes were seen in a few glomeruli. Aside from these inflammatory changes, the process may be interpreted as severe acute arteriosclerosis, according to Bell and Clawson. The term "malignant," they stated, may be properly applied to the nine cases of hypertension with acute uremia, but it is ill adapted to describe all cases of hypertension with uremia. They failed to find any definite changes in the skeletal muscles and the skin.

It is clear that the majority of the investigative work in this class of vascular disease has been directed at the kidney. Undoubtedly this results from the facts that the kidneys are always the seat of profound changes and that changes in the kidney are more likely to excite functional disturbances than changes in other organs. For it is evident that a severe arteriosclerosis may develop in an organ such as the spleen without any functional deficiencies being felt by the patient, while the same changes in the kidney would lead to advanced renal failure.

Keith, Wagener and Kernohan [3] were the first in this country to emphasize and clearly define the clinical features of malignant hypertension. They described the typical retinal changes occurring in patients with excessive hypertension, and the rapid downward course in conjunction with the functional failure, not of one organ, but of several organs simultaneously. They pointed out that the malignant hypertension may occur in young persons, or may be superimposed on a previous general arteriosclerosis or benign hypertension. It was found that the chief disturbances were in the retina, brain, heart and kidney. Typical symptoms of renal failure and of disease of the coronaries were infrequently found in their series. Of their eighty-one patients, seventy-four died within fifty-one months, and the majority within two years. Autopsies were done in seven cases. Microscopically, the most outstanding features were the diffuseness of the lesions and the degree of involvement of the smaller arteries and arterioles, while the larger arteries and capillaries were free from changes. All organs and tissues, even the arterioles of the skeletal muscles, were severely involved. In every case the kidneys showed profound changes. The walls of the smaller arteries and arterioles were thickened and the lumina were narrowed. The thickening, the writers stated, was due to hyperplasia of the intima with hypertrophy and splitting up of the intimal elastic lamina, as seen in arteriosclerosis. In addition, they found hypertrophy

of the muscular tissue of the media as well as an increase of fibrous tissue of the adventitia in all their cases. In no case did they find necrotic changes in the arterioles. In places the arteriole lumen was obliterated, due to the intimal hyperplasia and hypertrophy of the media. The almost total absence of signs of degeneration in the intimal layer of the smaller arteries and arterioles led them to believe that this process was distinct from simple arteriosclerosis. In a later report, Anderson, Kernohan and Keith [20] described an intermediate group, composed of cases of the severe benign or early malignant type. The cardiac, retinal and renal functions were remarkably good; the peripheral arterioles showed involvement equal to that in the malignant group.

In our series of cases we were able to confirm in general the clinical observations described by Keith and his associates under the term "malignant hypertension." Typical retinitis, a persistent excessive hypertension and a simultaneous functional break-down of more than one vital organ were prominent features. Headache and rapid loss of strength and weight were the two striking symptoms. Keith and his co-workers observed that anemia was absent in their series of cases; we were unable to confirm this, as anemia was practically always present in our cases, especially in the later stages of the disease. Renal failure was a more conspicuous observation in our series than in those described by Keith, Wagener and Kernohan; this difference may be ascribed to the fact that more of our cases were seen in terminal stages. The clinical differentiation between chronic glomerular nephritis with renal failure, and malignant hypertension with renal failure may be difficult unless one knows what has gone on before the patient comes under observation, although when renal failure develops in the course of malignant hypertension the downward progress is much more rapid than in chronic glomerular nephritis. Furthermore, definite remissions are likely to occur in the course of chronic nephritis, while in malignant hypertension there are no remissions; progress downward is so rapid that it appears justifiable to call this the most malignant of all renal diseases.

Histologically, our observations correspond essentially with those of Keith and his associates. We found numerous types of histologic changes in the smallest arteries and arterioles of the kidneys, pancreas, spleen and liver. Frequently larger arteries of the organs participated in the same process. Although a variety of lesions were seen, even in the same microscopic section, the general features were those of arteriosclerosis. Occasionally, the walls of one of the smallest arteries or

20. Anderson, E. W.; Kernohan, J. W., and Keith, N. W.: Histologic Studies of the Peripheral Arterioles in Ambulatory Patients with High Blood Pressure, Proc. Staff Meetings Mayo Clinic **3**:314, 1928.

arterioles were found almost completely transformed into homogeneous mass consisting of hyaline and fatty changes, while an adjacent vessel in the same microscopic area showed hyperplastic elastic thickening of the intima with connective tissue proliferation. Often but not constantly these processes were found combined in the same vessel. At times the media and adventitia of the smallest arteries and arterioles were found to be thickened, but such changes existed in conjunction with arteriosclerosis of the same vessel or of those adjacent to it. Medial hypertrophy was less conspicuous when the arteriosclerotic process was an advanced one. In some cases necrosis was present in the walls of the afferent glomerular arteriole and of the loops of the corresponding glomeruli. When present, the necrosis appeared to be a part of an already existing severe arteriosclerosis. In some cases the necrotic changes were widespread and numerous, and in others they were few and scattered. In cases in which the necrotic process is extensive, the changes excited in the glomeruli and surrounding tissues resemble those of inflammation. Fahr [11] claimed that this is an added inflammatory process; Herxheimer,[13] Jores [21] and Löhlein [14] expressed their belief that it is a severe degree of arteriosclerosis. Severe arteriosclerotic changes may be found in cases of chronic glomerular nephritis, as has been pointed out by Fishberg.[22] This fact may occasionally lead to difficulty in interpretation of the histologic changes.

With respect to the changes in the media of the arterioles of the skeletal muscle, various degrees of thickening were found. Frequently the change consisted of a medial thickening leading to a pronounced narrowing of the lumen; occasionally no definite change was found, and at times it was difficult to state whether a thickening existed or not.

Clinically, it appears that malignant hypertension is a later phase of benign hypertension, differing from the benign form in the greater severity of its symptoms, the more rapid functional break-down of the essential organs of the body and the more persistent and more excessive hypertension. Some patients who have had benign hypertension for years may, for unknown reasons, develop the malignant form.

The assumption that malignant hypertension is characterized by a generalized vascular disturbance affecting the smallest arteries and arterioles of the entire body appears to be correct. It is seen in case 7 that cerebral hemorrhage terminated the course of the disease and that on examination of the kidney profound changes, including a few

21. Jores, L.: Ueber den pathologischen Umbau von Organen, Virchows Arch. f. path. Anat. **221**:14, 1916.

22. Fishberg, A. M.: The Arteriolar Lesions of Glomerulo-Nephritis, Arch. Int. Med. **40**:80 (July) 1927.

areas of necrosis, were found. One may assume that had the cerebral accident been postponed for a time, renal necrosis might have progressed far enough to produce renal insufficiency.

Morphologically, the lesions of malignant and benign hypertension are of the same general pattern. The striking changes in both forms are arteriosclerotic. The arteriosclerotic process of the malignant type not only affects the larger and smaller arteries, but involves the smallest arteries and the arterioles of almost the entire body. In the malignant form the lesions appear to be progressing more rapidly, producing a greater narrowing of the lumina and leading to more profound functional disturbances in the essential organs of the body. The hypertrophy of the musculature of the arterioles may be changes of adaptation due to strain imposed by hypertension. The chief difference between the benign and the malignant form of hypertension appears to be one of degree.

CONCLUSIONS

1. Sixteen cases of malignant hypertension are analyzed. Of the sixteen patients, thirteen died and on twelve autopsy was done.

2. Clinically, the chief observations were headache, a profound loss of weight, a persistent excessive hypertension, functional failure of one or more essential organs, a progressively downward course and a rapid termination. A characteristic retinopathy was present in all cases.

3. Histologically, the essential lesions were arteriosclerotic. The smallest arteries and arterioles were almost universally involved. In six cases necrotic lesions had developed in the walls of the afferent glomerular arterioles and in the loops of the corresponding glomeruli. Hypertrophy of the media of the arterioles of the skeletal muscles was usually found. In the arterioles of the kidneys and other organs, medial hypertrophy was found occasionally, in association with arteriosclerotic changes.

4. The clinical and morphologic observations on malignant hypertension differ from those on hypertension of benign form only in degree. Greater severity of the clinical symptoms and a more extensive and destructive form of lesion of the smallest arteries and arterioles are characteristic of malignant hypertension.

REPORT OF CASES

CASE 1.—H. L., a white bartender, aged 34, was first observed by us in February, 1928. His chief complaint was headache and loss of weight. In March, 1924, he began to lose weight and strength; on examination the only positive observation was hypertension of 210 systolic, 115 diastolic. During the following four years the blood pressure varied from 180 systolic, 110 diastolic to 220 systolic, 130 diastolic. In the early summer of 1928, he became worse. Headache, visual disturbances and cramps developed, and he entered this hospital on July 10.

The blood pressure was 250 systolic, 135 diastolic. The radials were tense and wiry, and the vessel walls were thicker than normal. Renal function was definitely impaired. No cardiac enlargement was found. No murmurs were heard. The abdomen appeared normal, although the abdominal cramps were more troublesome than the severe headaches. Ophthalmoscopic examination revealed: bilateral choked disks, more severe in the right eye than in the left; fresh hemorrhages throughout both retinas; atrophic changes more pronounced in the right eye than in the left. The Wassermann reaction of the blood was negative. The disease made rapid progress, and renal function steadily declined. The headaches and the cramps became worse. On July 25, uremia without convulsions set in, and the patient died on July 26.

Observations at autopsy were: Both kidneys were larger than normal, and the surfaces were smooth; the right one weighed 175 Gm., and the left 170 Gm. Over the surface of both kidneys were many petechial hemorrhages, giving the appearance of the "flea-bitten" kidney. On section, considerable blood was seen in the pelvis of both kidneys; large petechial hemorrhages were numerous throughout the pelvic mucous membrane. The markings were well defined, and the pallor of the cortex and columns of Bertini stood out in sharp relief against the darker medullary portion. A moderate thickening of the walls characterized the renal arteries and their larger branches. Microscopically, many glomeruli appeared normal; others had the appearance of an embolic focal glomerulonephritis. Some of the glomerular loops had undergone necrotic changes, while other loops appeared normal. There was a cellular exudate in Bowman's capsular space, and definite epithelial-like crescents were found in places. Examination of the arterioles revealed a necrosis of the wall of the afferent glomerular arterioles, corresponding to the necrotic glomeruli. Not all the arterioles showed necrosis. In some there was profound intimal thickening produced by fatty degeneration, connective tissue proliferation or hyaline change, leading to partial occlusion of the lumen in some places and to complete occlusion in others. In some areas the media shared in the degenerative changes found in the intima. Although the media of smaller arteries and arterioles occasionally seemed thicker than normal, this was found to be the effect of an extension of a fatty degeneration of this layer. Frequently an endarteritis of the smaller arteries was found, with a fatty degeneration of the media. Throughout the smaller arteries the elastic tissue was proliferated. In the interstitial connective tissue surrounding some of the smallest arteries and arterioles there was perivascular leukocytic infiltration. The thickened adventitia was found to be free from these changes. In the tubules there was slight fatty degeneration of many epithelial cells. This fat did not doubly refract polarized light. In the cortex there were definite areas of leukocytic infiltration. Intimal thickening was present in the smaller arteries and arterioles of the liver, causing almost complete obliteration of the lumen in places. Fatty and hyaline degeneration predominated, with atrophy of the media. In some places the intimal degenerative changes were mild, and here the media appeared thickened. The same type of degenerative changes were found in the spleen as in the liver, except that they appeared to be more severe; no necrosis of the walls was found in the spleen.

Case 2.—J. L., a white laborer, aged 42, entered the hospital on Aug. 22, 1928, complaining of severe headache, dizziness, weakness and palpitation of the heart. He had been in the hospital in June, 1920, and had had a herniotomy done under local anesthesia; blood pressure at that time was 220 systolic and 120 diastolic, and the urine, heart and renal function were apparently normal. At that time the patient had no complaint referable to the hypertension. On reentrance to the hospital, his blood pressure was 255 systolic and 160 diastolic. The radial and

temporal arteries were wiry and tortuous. Renal function was normal. Ophthalmoscopic examination revealed areas of old organized infiltrates in the fundi; many yellowish white spots and recent hemorrhages were seen in the macular areas. The Wassermann reaction of the blood was negative. The headaches and weakness became worse. The patient lost weight rapidly; from an average of 215 pounds (97.5 Kg.), his weight had diminished to 160 pounds (72.5 Kg.) on his entrance to the hospital, and he weighed about 128 pounds (58 Kg.) at death, which occurred on Feb. 3, 1929, from bronchopneumonia and heart failure.

Autopsy revealed that the heart was large and weighed 655 Gm. The wall of the left ventricle measured 33 mm. The aortic leaflet of the mitral valve contained an atherosclerotic patch. Pronounced atherosclerosis was found in the aorta. The coronaries had lumina of normal size. Both kidneys were smaller than normal; the right one weighed 117 Gm., and the left 134 Gm. They were granular. On section, the cortex was found to be thinned; there were many hemorrhagic areas in the pelvic mucosa, and considerable blood was found in the pelvis. The renal arteries were thickened and arteriosclerotic. Microscopic examination showed that many glomeruli were intact; the loops were normally filled with blood. Other glomeruli had undergone fibrosis, hyalinization or atrophy. A few showed distinct necrosis of some of the loops, and the afferent arteriole revealed the same necrotic changes. Most of the arterioles and the smallest arteries had degenerative and proliferative changes in the intima, with atrophy of the media. Fatty degeneration extended from the intima into the media in some places. Endarteritic lesions were numerous, occasionally leading to obliteration of the lumina. In some areas the media of the arteriolar wall was profoundly thickened and the intima appeared to be intact. The adventitia was found to be universally thickened. The lumina of the arterioles were narrowed throughout and frequently occluded. There was fatty degeneration of the epithelial cells of the convoluted tubules, and some of the fat doubly refracted polarized light. There was an increase of the interstitial tissue of the kidney. Sections from the pectoralis major and diaphragm showed many arterioles to be occluded; the intima was normal. Extensive hypertrophy of the media was found. The vessels of the lungs were normal. No changes were seen in the arterioles of the brain. The media of the smallest arteries was normal.

Case 3.—M. D., a white woman, aged 41, was first observed in 1920, when a breast was amputated for a tumor, which proved to be benign. At that time the blood pressure was 160 systolic, 110 diastolic, and the heart and kidneys were normal. She came under observation again in March, 1924, because of weakness, headache and dizziness. The blood pressure was 215 systolic and 120 diastolic. Arteriosclerosis of the retinal arteries was found, but no edema or hemorrhages were seen. The radial arteries were thickened. The heart was enlarged; the urine was normal, as was the nitrogen content of the blood. In June, 1928, the patient reentered the hospital complaining of pain in the back of the neck, referred over the back of the head. She had lost 40 pounds (18.1 Kg.) and was very weak. Nocturia, albuminuria, palpitation of the heart and vomiting had set in. At first the renal function was good, but it began to fail gradually. Aside from enlargement, the heart was normal. There was no edema. Ophthalmoscopic examination revealed hemorrhagic areas in both fundi, and moderate edema of both retinas. The Wassermann reaction of the blood was negative. During the following four months, the symptoms became exaggerated, and vomiting became pronounced. The patient died in true uremic coma on October 4.

At autopsy, both kidneys appeared reduced in size and coarsely granular. The right kidney weighed 110 Gm., and the left 132 Gm. On section, the peripelvic fat was seen to be increased. In the cortex, and especially at the corticomedullary boundary zone, the arteries stood out prominently. The renal artery and its main branches were abnormally thickened, so that the lumina were reduced in size. Microscopically, numerous glomeruli appeared normal; others were hypertrophied, and many had undergone complete hyalinization or necrosis. Fatty degeneration was found in some of the partially obliterated tufts. There was profound thickening of the walls of the smallest arteries and arterioles. In places the entire wall was hyalinized, and occasionally necrosis was found. This necrotic process extended into the hilus of the glomerulus, leading to necrosis of the corresponding loops of the glomerulus. Erythrocytes were seen to infiltrate the walls of a few necrosed arterioles. Periarterial leukocytic infiltration was present in the adventitia and in the interstitial connective tissue surrounding some of these vessels. Some arterioles were characterized by fatty degeneration of the entire wall. Throughout the kidney the lumina of the smallest arteries and arterioles were narrowed, almost obliterated in areas. The thickening of the walls was chiefly due to intimal degenerative changes. Frequently, the intimal changes extended into and involved the media. There was a definite increase in the elastic tissue throughout the vessels. In no arteriole of the kidney could hypertrophy of the media be made out. In the liver, the lumina of the smallest arteries were narrowed as a consequence of the thickening of the vessel wall. The intima was almost universally thickened because of fatty and hyaline degeneration and proliferation of connective and elastic tissue. In most areas the media was thinned, while in some places the media and the adventitia were definitely thicker than normal. In the epithelial cells of the tubules there was considerable fatty degeneration; none of the fat was doubly refracting. An increase of interstitial fibrous tissue was present and there were areas of cellular infiltration. In the pancreas, the intima of the smaller blood vessels was thickened. In some vessels there was thickening of the media and adventitia, although some of the smaller arteries showed degenerative changes in the media. Fibrous tissue proliferation, fatty degeneration and hyalinization were present in the same vessel wall. In some of the smallest arteries of the spleen, fatty degeneration of the intima and thickening of the media with widening of the lumina was found; in others, with the same degree of fatty degeneration, the media was thicker than normal, with narrowed lumina. Some of the smallest arteries showed no intimal changes, but there were hypertrophic and proliferative changes in the media and adventitia. The elastic tissue was universally hyperplastic. The arterioles and smallest arteries of the lungs were normal. In the pectoralis major muscle the media was hypertrophic in places, although some of the arterioles appeared normal.

Case 4.—A. K., a white laborer, aged 57, entered the hospital on Dec. 2, 1926, complaining of headache, dyspnea and weakness for the previous year. The symptoms had gradually become worse until one month prior to entrance, when the headache and weakness became so severe that he was confined to bed. His weight, which normally was 160 pounds (72.5 Kg.), gradually diminished; on his admission to the hospital it was 100 pounds (45.3 Kg.). The blood pressure was 240 systolic and 150 diastolic. The radial vessels were tortuous, thickened and wiry. Renal function was greatly reduced. Aside from a moderate enlargement, the heart was normal. Ophthalmoscopic examination showed a moderate retinal edema of both fundi, with numerous hemorrhagic areas. The Wassermann reaction of the blood was four plus. On Jan. 14, 1927, he became weak, developed pulmonary edema and died of uremia.

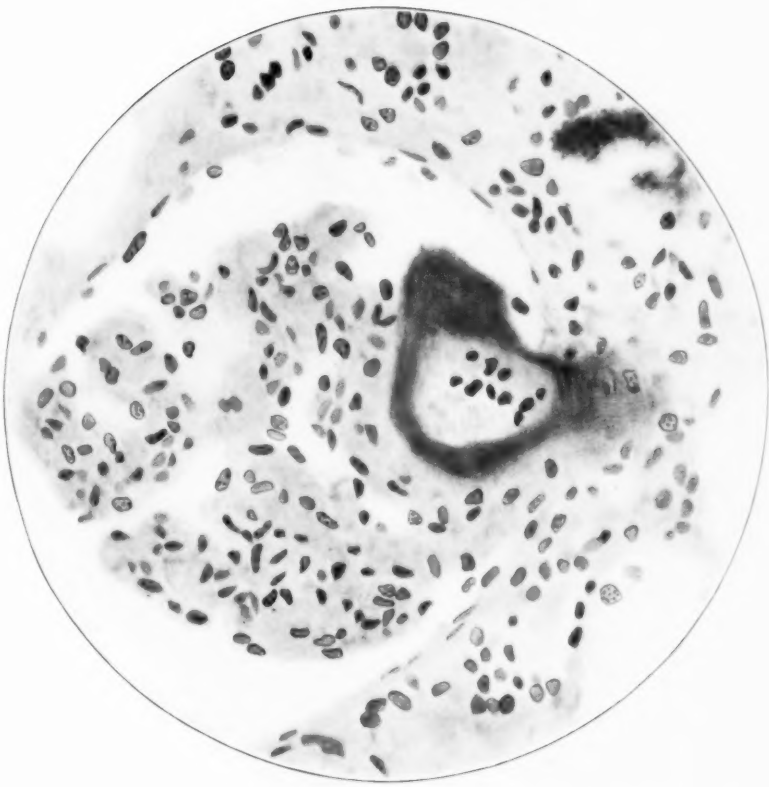

Fig. 1 (case 1).—A glomerulus showing necrosis of the afferent arteriole with extension into the glomerular loops. Hematoxylin and eosin stain; × 500.

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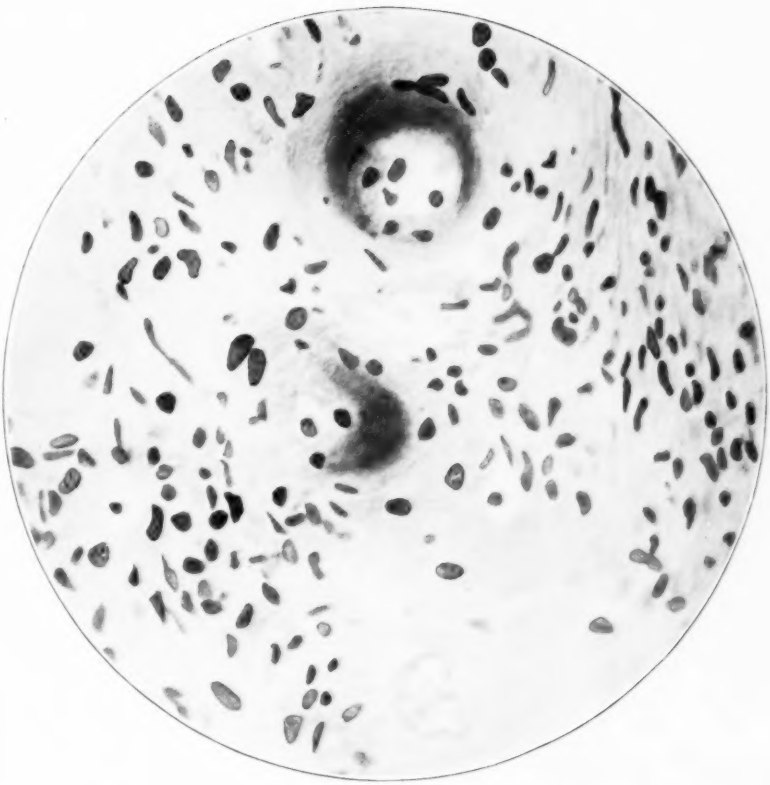

Fig. 2 (case 2).—Arterioles from the kidney, illustrating necrosis of the walls. Hematoxylin and eosin stain; × 500.

At autopsy the heart weighed 500 Gm.; the valves were normal. Both kidneys were greatly contracted. The right kidney weighed 41 Gm., and the left 64 Gm. They were coarsely granular. On section, the peripelvic fat was found to be increased. The cortex was thinned, and the markings were obscured. Microscopic examination showed widespread fibrosis of the glomeruli. In places the glomerular capsule was thickened with fibrous tissue. The loops in some areas

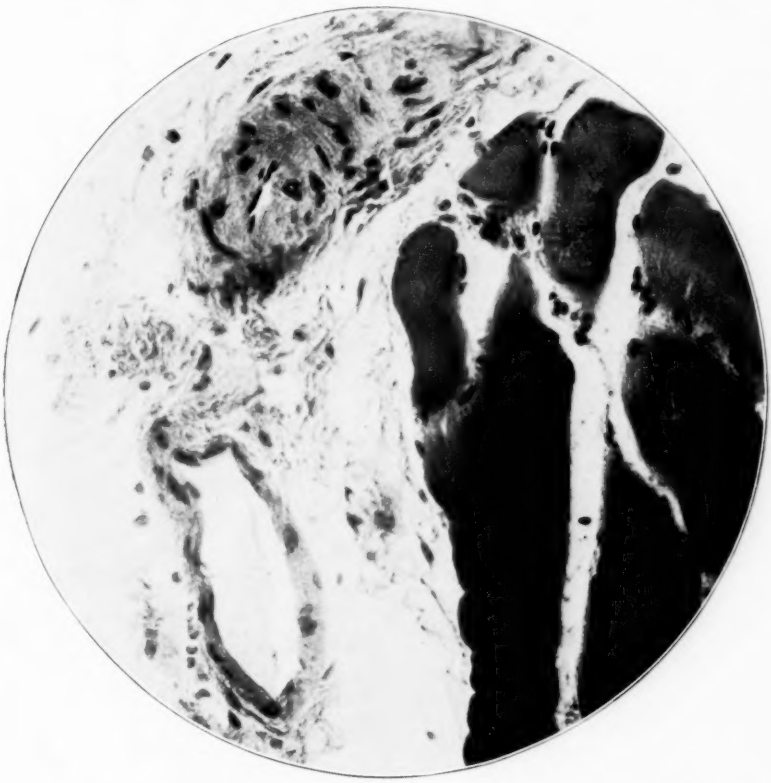

Fig. 3 (case 2).—An arteriole from the pectoralis major muscle showing hypertrophy of the media and narrow lumen. Hematoxylin and eosin stain; × 450.

contained blood. The arterioles were universally narrowed, due to thickening of the arteriolar wall. This thickening was produced chiefly by connective tissue proliferation of the intima. Occasionally, hyaline or fatty degeneration was seen in the intima. Elastic tissue hyperplasia was pronounced throughout the arterial tree. A moderate thickening of the media of many arterioles was seen. In the walls of numerous afferent arterioles there was a necrotic process extending into

the loops of the glomerulus. In the interstitial tissue surrounding these necrosed vessels there were areas of lymphocytic infiltration. Exudative and proliferative changes were found in the tuft. Fatty degeneration of the epithelial cells of the convoluted tubules was present. The interstitial tissue was increased. Examination of the liver showed portal cirrhosis. There was an advanced arteriosclerosis, involving the smaller and smallest arteries and arterioles of the liver. Occasion-

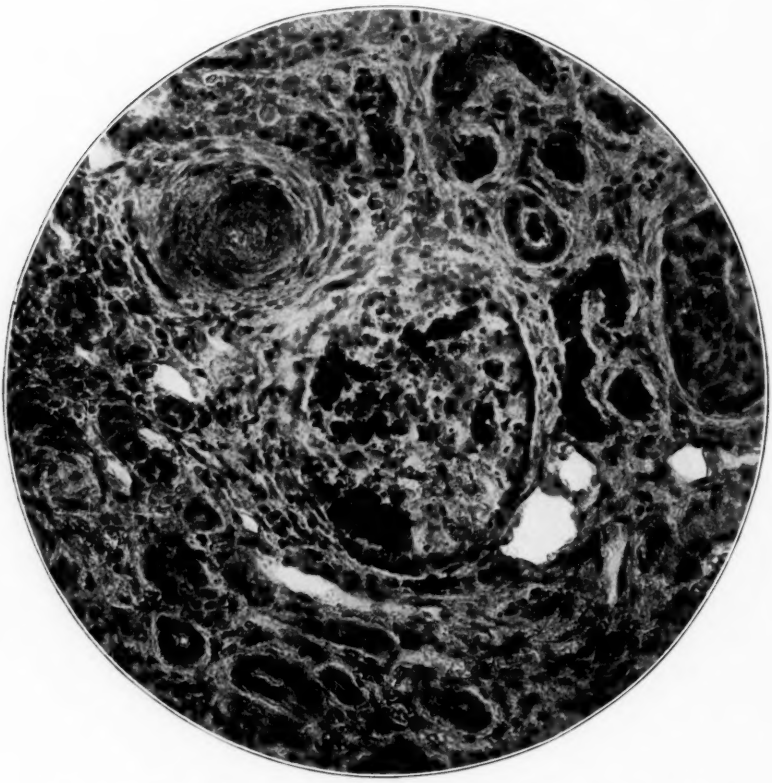

Fig. 4 (case 3).—A small artery and a glomerulus. The lumen of the small artery is obliterated and the necrotic wall is infiltrated with red blood cells. The glomerulus shows areas of necrosis.

ally there was medial hypertrophy. The vascular changes in the spleen resembled those in the liver. The smallest arteries and arterioles of the lung were normal.

Case 5.—M. B., a white laborer, aged 53, was admitted to the hospital on Nov. 7, 1926, complaining of headache, dyspnea and loss of weight for the previous three months. The blood pressure was 190 systolic and 120 diastolic. The radial and temporal arteries were tortuous and of the pipe-stem variety. Renal function was greatly reduced. Aside from a pronounced enlargement to the left and a

systolic aortic murmur, the heart was normal. Ophthalmoscopic examination revealed that the veins were full and the arteries tortuous and thinned; considerable edema around both disks and numerous hemorrhagic areas along the course of the arteries were found. The Wassermann reaction of the blood was four plus. The weakness, loss of weight, and headache became worse. Renal function rapidly failed, and a true uremia developed with some twitching but no convulsions. The patient died on Jan. 25, 1927.

At autopsy the heart was enlarged, weighing 480 Gm. The left ventricle was twice as thick as normal. There were no defects of the valves, except atherosclerosis of the aortic cusps, which was a part of the extensive atherosclerosis of the aorta. Both kidneys were contracted and granular; the right weighed 65 Gm., and the left 70 Gm. The walls of the larger arteries were thickened and the lumina were narrowed throughout. On section, the pelvic areas were filled with fat. Microscopic examination showed that many glomeruli were fibrosed or hyalinized. In some of them there were remnants of old epithelial crescents. Many glomeruli appeared normal. Numerous loops of many glomeruli were undergoing necrosis; necrotic changes were found in the afferent arterioles corresponding to the loops. In many arterioles the intima was the seat of fatty degeneration; but the outstanding change was proliferation of the intimal connective tissue. The arteriosclerotic process caused narrowing of the lumina in places, and in other areas the lumina were completely obstructed by endarteritis obliterans. In no place could medial hypertrophy be seen; medial atrophy was universal. Interstitial connective tissue was increased, and a plasma cell infiltration, with fixed tissue proliferation, was found. There was fatty degeneration of the epithelium of the convoluted tubules. This fat did not doubly refract polarized light. In the spleen there was an increase in the connective tissue. Pronounced arteriosclerosis was seen; there was complete hyalinization of the walls of many arterioles, with occlusion of the lumina. Fatty degeneration was present. The liver, arteries and arterioles also were arteriosclerotic. Medial hypertrophy was seen in arterioles of the liver and the spleen.

Case 6.—R. M., a white man, aged 52, was admitted to the hospital on July 26, 1925, complaining chiefly of headache, dyspnea and palpitation of the heart. Until the onset of the present trouble, he had always been well. His blood pressure was 230 systolic and 100 diastolic. The radial arteries were thickened. Renal function was reduced. The heart was enlarged to the left, and there was an apical systolic murmur transmitted to the axilla. Ophthalmoscopic examination showed an increase in the light reflex of the arteries, with moderate retinal edema; hemorrhages, old and recent, were present. The Wassermann reaction of the blood was negative. On Dec. 16, 1926, the patient died of apoplexy.

Autopsy revealed that the heart weighed 565 Gm. Left ventricular hypertrophy was marked. The valves were normal. Both kidneys were decidedly contracted and coarsely granular; the right one weighed 94 Gm., and the left 102 Gm. The peripelvic fat was increased. In places the demarcation between cortex and medulla could not be seen; the cortex was remarkably thinned. Microscopically, extensive glomerular atrophy was found; many glomeruli were fibrosed, others hyalinized. A few glomeruli had necrotic loops corresponding to necrosis of the afferent glomerular arterioles. Proliferation of Bowman's capsule and an increase in cellular elements were outstanding features. A few epithelial crescents were present. The smaller arteries and arterioles were characterized by connective tissue proliferation in the intima. In a few, fatty degeneration of the intima was found. Occasionally, there was necrosis of the arteriolar wall. The

smaller vessels were universally narrowed. Hypertrophy of the media in the arterioles was seldom found. Elastic tissue was increased. The larger arteries of the kidney were arteriosclerotic. In the larger arteries, including the renal, decided arteriosclerosis had occurred, with medial atrophy. Many tubules had become completely replaced by connective tissue; the epithelium lining the convoluted tubules had undergone cloudy swelling, but little fatty degeneration was found. An extensive increase of the interstitial connective tissue had occurred. Definite arteriosclerosis with narrowed lumina and medial atrophy characterized arteries of all sizes in the liver. Similar changes were present in the spleen and the pancreas.

Case 7.—C. D., a white man, aged 32, entered the hospital on Dec. 9, 1926, because of a slight cerebral hemorrhage. In 1918 he was denied admission to the U. S. Army on account of hypertension. At that time he was told that his blood pressure was 200. According to the history, subsequent examinations revealed no albuminuria or any other defect except the hypertension, which persisted around 200. On entrance to the hospital his blood pressure was 205 systolic and 130 diastolic. The radials were small and cordlike, and the walls were thicker than normal. Renal function was good. Aside from enlargement to the left, the heart was normal. Ophthalmoscopic examination showed many retinal hemorrhages with moderate papilledema in the retina. The Wassermann reaction of the blood was negative. On May 31, 1927, there was another cerebral hemorrhage which caused death.

Autopsy revealed that the heart was enlarged and weighed 585 Gm. Left ventricular hypertrophy was pronounced. No disease of the valves was found. Profound atherosclerosis was present in the aorta and in the coronaries, but there was no coronary occlusion. Both kidneys were smaller than normal and coarsely granular in appearance; the right kidney weighed 132 Gm., and the left 118 Gm. The walls of the main renal arteries were thickened with an atherosclerotic process. On section, the cortex appeared to be thinned and the markings were obscured. Microscopic examination showed that the glomeruli in general were well preserved. Frequently, fibrosed and atrophic tufts were found adjacent to a normal glomerulus. A striking feature was the finding of necrosed loops in some glomeruli; in addition to the necrosis of the loops, cellular exudation and the formation of epithelial crescents had occurred. The smallest arteries and arterioles were universally diseased. Many of them were occluded because of the thickened vessel wall. The chief changes were hyaline and fatty degeneration of the intima, which frequently involved the media. In places there were endarteritic changes, with fatty degeneration of the media. There were areas of arteriolar necrosis; other areas showed complete obliteration of the arterioles, associated with hyaline and fatty changes that appeared to be progressing toward necrosis. The adventitia was thickened throughout. No medial hypertrophy was found. There was cicatrization of the interstitial tissue. The tubular epithelial cells had undergone cloudy swelling and fatty degeneration, but the fat did not doubly refract polarized light. The vessels of the lungs were normal. The extensive arteriosclerotic process found in the kidney was present also in the arteries and arterioles of the liver. There was no necrosis of the vessels of the liver. Occasionally, hypertrophy of the media was found in a small artery and arteriole. There was a well developed arteriosclerotic process in the spleen similar to that seen in the kidney.

Case 8.—L. P., a white school girl, aged 17, began to complain of headache and vomiting in July, 1927. These symptoms progressively became worse until November, 1927, when she developed a profound visual disturbance. An oculist

found choked disks and retinal hemorrhages and he suspected tumor of the brain. On Nov. 30, 1927, the blood pressure was 270 systolic and 155 diastolic. The radial and temporal arteries were cordlike and hard to compress. There was no renal insufficiency. No cardiac enlargement was found and the heart was normal. Urinalysis revealed bloody urine; later the condition entirely cleared up. Ophthalmoscopic examination showed bilateral choked disks, with many petechial hemorrhages in the periphery of the retina; the veins were full, and the arteries thin and straight. The headache and vomiting became worse. By March, 1928, the patient had lost 25 pounds (11.3 Kg.). Severe epigastric pain developed and recurred periodically; morphine was necessary for relief. The Wassermann reaction of the blood was negative on several occasions; the father died of syphilis and the mother gave a four plus Wassermann reaction. Renal apoplexy developed in May, 1928. Hematemesis occurred during the final week of illness. The patient died in true uremia on June 2. The heart showed slight hypertrophy of the left ventricle, but there were no defects of the valves. The right kidney was smaller than normal, weighing 95 Gm. It had a coarsely granular surface. The renal artery was thickened, and on cut section the smaller arteries stood out prominently. In the pelvis there was considerable old blood, and in the mucosa many recent petechial hemorrhages were seen. The cortex was thickened and the corticomedullary markings were obscured. Histologic examination showed the glomeruli to be well preserved; some were sclerosed, while others had undergone hyaline or fatty degenerative changes. Occasionally a glomerulus was seen in which some of the loops were converted into a granular and cellular mass without erythrocytes. The arterioles were universally diseased. The lumina were universally narrowed and in some places completely occluded. The changes in the arterioles for the most part were in the intima which was thickened; the media was occasionally found to be thickened. Adventitial thickening was universally present. Fatty degeneration of the intima of the arterioles was widespread, frequently extending into and involving the media. The connective tissue was increased in the adventitia and in the intima. In the smaller arteries the elastic tissue was hyperplastic. In no place were there necrotic changes in the arterioles or in the glomeruli. In some areas there was advanced fatty degeneration of the cells lining the convoluted tubules; many tubules were atrophied and were undergoing replacement by connective tissue. In the pectoralis major muscle, the media of the small arteries and arterioles was profoundly thickened, almost occluding the lumen in some areas; the intima was intact. The outstanding change in the liver was a general hypertrophy of the media of the arterioles; the intima was generally intact. In the spleen the arteriolar wall was found to be completely hyalinized in places; in other places it was thickened, due to medial hypertrophy. The intima was normal in most areas. The smallest arteries and arterioles of the lung were normal.

Case 9.—D. D., a white girl, aged 10, entered the hospital on Sept. 3, 1927, complaining of persistent headache, dizziness and insomnia for the previous year. The following data were abstracted from the records of over two years' study in the hospital and in the outpatient clinic: The blood pressure was 205 systolic and 155 diastolic on admission to the hospital. Several convulsive seizures developed immediately prior to entrance. The radials were cordlike and thickened. Renal function remained unimpaired. There was a pronounced enlargement of the heart to the left, and a systolic mitral murmur was heard. On ophthalmoscopic examination of the right eye, the disk appeared normal in size and color; the arteries were very thin and not tortuous. Many hemorrhages were seen to follow the course of the arteries. The same condition was seen in the left eye, except that

the macular area was free from change. The Wassermann reaction of the blood was negative. Under treatment, during the two years of observation, the blood pressure came down to as low as 130 systolic and 70 diastolic. On April 4, 1928, there was a sudden rise in blood pressure to 260 systolic, 150 diastolic. Renal apoplexy developed on October 16, and the blood pressure was 228 systolic and 170 diastolic. Anemia was present at times in the course of the disease. Heart failure slowly developed, which caused death on May 27, 1929. The heart was enlarged and weighed 315 Gm. The left ventricular wall measured 1 cm. Both kidneys were contracted and granular; the right weighed 75 Gm., and the left 25 Gm. Microscopic examination showed the loops of many glomeruli to be well filled with blood. Occasionally a glomerulus was found with an exudate in Bowman's capsular space, with thickening of the capsule. No necrotic loops were seen, and many glomeruli had undergone atrophy. Practically all the arterioles were narrowed and many obliterated. The chief change was an intimal connective proliferation, although fatty degeneration of the intima was occasionally seen. The elastic tissue of the smallest arteries had undergone hyperplasia. Frequently the endothelial cells of the intima were increased. In some vessels such changes would be present in an otherwise normal vessel, and in others a degeneration of the media and intima were found. The media of the arterioles and the smallest arteries varied in appearance; in some the media was thicker and in others decidedly thinner than normal. The epithelium of the tubules was universally swollen and undergoing granular degeneration. Fatty degeneration was extensive around the central veins of the liver. A distinct hypertrophy of the media of the smallest arteries and arterioles was seen, which practically occluded the lumina in places. Slight intimal degeneration was found. The arteries and arterioles of the spleen were profoundly diseased. In most of them the lumen was reduced to a considerable degree; in others complete occlusion had occurred. The thickening of the walls was confined almost entirely to the intima which was occupied by hyaline substance. The entire vessel wall was occasionally converted into a homogeneous mass. Some of the arteriolar walls were degenerated with fat deposits. In a few arterioles the fat did not border the lumen, but appeared between the media and the proliferated intimal tissue. Some of the smaller arteries of the pancreas showed medial hypertrophy; otherwise, the changes resembled those found in the liver. Sections from the pectoralis major showed the adventitia and media so extensively thickened that the lumen was almost obliterated; the intima appeared normal. In the lungs the walls of many of the arterioles were thickened, due to hypertrophy of the media. In places the lumina were almost occluded.

Case 10.—G. H., a colored woman, aged 56, was admitted to the hospital on Nov. 8, 1928, complaining of vomiting, dyspnea and exhaustion. According to her daughter, the patient had had high blood pressure for the previous five years. The urine, she said, had been free from albumin until the present "break-down," which occurred early in October, 1928. The blood pressure was 235 systolic and 120 diastolic. The radials were thickened, tortuous and full. Renal function was definitely impaired. Extensive hypertrophy of the heart was found. Generalized transient edema was present. Ophthalmoscopic examination showed the disks and media to be hazy; the macular area had atrophic and fresh choroidal exudate with pigment. The veins were full, and the arteries thin and tortuous. Numerous hemorrhages were visible in both retinas. The Wassermann reaction of the blood was negative. On June 4, 1929, the patient died of heart failure.

At autopsy, the heart was eccentrically hypertrophied to the left, and weighed 480 Gm. Aside from a moderate thickening of the mitral valve, no defect was found. Both kidneys were contracted and granular; the right one weighed 29

Gm., and the left 70 Gm. On cut surface, the cortex was very thin and the markings practically obliterated. Many small hemorrhages were found in the pelvic mucosa. The largest and smallest arteries were prominent and their lumina were decidedly narrowed. Microscopically, many glomeruli appeared normal; some were congested. In places Bowman's capsules were thickened from an increase in connective tissue, causing the glomerular loops to appear as if clothed in a shell of connective tissue. There were areas of leukocytic infiltration in the cortex. No areas of necrosis were found in the glomerular loops. Many of the smallest arteries and arterioles were occluded by thickening of the intima. The intimal thickening consisted of fatty degeneration; in others, there was no fatty degeneration but proliferation of connective tissue was seen, with elastic tissue hyperplasia. Frequently these intimal changes occurred together, and in places the media as well as the intima was involved. Despite the universal and profound degenerative changes present there were no arteriolonecroses. Hypertrophy of the media was not seen. Fatty degenerative changes were found in the convoluted tubules; many tubules had become replaced by fibrous tissue. A pronounced endarteritis obliterans was present in some arterioles of the liver. No medial hypertrophy was seen. Arteriosclerosis of the type described for the kidney was the striking feature of both the liver and spleen. Sections from pectoralis major and diaphragm showed that the media was hypertrophied, the lumina greatly narrowed and the intima normal. The larger arteries of the body were uniformly thickened. The chief changes consisted of hyperplasia of the connective and elastic tissues of the intima, with increase of the adventitial tissue. The media appeared normal.

Case 11.—L. C., a white housewife, aged 42, entered the hospital on Dec. 27, 1928, complaining of headache and pains in the back, arms, legs and chest for the previous eight months. She had entered the hospital on April 4, 1927, and had undergone an operation. The records showed that the blood pressure at that time was 190 systolic and 100 diastolic; the urine was normal. The blood pressure on last admittance was 230 systolic and 115 diastolic. The radials were wiry and hard to compress. Renal function was moderately reduced. Cardiac enlargement was pronounced. No edema was present. Ophthalmoscopic examination showed a choked disk in the left eye; the arteries were thin and tortuous. The vessels were pinched off in the disk, and pulsations were observed in the superior vessels. The right eye was about the same as the left except for some hemorrhagic areas. The Wassermann reaction of the blood was negative. There was a rapid loss of strength and weight, and the headaches and pains became more pronounced. On Jan. 11, 1929, a convulsion set in and the patient died that night. At autopsy the heart appeared very large, weighing 612 Gm.; the valves were intact. Pronounced atherosclerosis was present in the aorta and coronaries; there was no coronary occlusion. The left kidney was cystic and weighed 19.5 Gm.; the right one weighed 137.5 Gm., and had a finely granular surface. On section, the cortex was found to be thinned, the peripelvic fat increased and the corticomedullary markings obscured. The striking feature was the prominence of the arteries through the cut surface; it could be seen with the naked eye that the arteries were almost obstructed from the thickened walls. On microscopic examination, many glomeruli appeared normal; the capillary loops were filled with blood. Others were atrophic and hyalinized. Fatty degeneration of Bowman's capsule was seen in the degenerating tufts. Numerous arterioles were occluded by intimal thickening produced by fatty and hyaline degeneration. The endothelial cells of the intima were proliferated in places, and behind this there was fatty or at times hyaline degeneration extending back into the media. In some of the smallest arteries there was hyper-

trophy of the media, existing alone, or in association with degenerative and proliferative changes in the intima. The elastic tissue was increased in the arteries, showing splitting of the internal elastic lumina. The larger blood vessels showed atherosclerosis with medial thinning. No necrotic arterioles were found. The tubules were almost completely replaced in some areas by fibrous tissue. Cloudy swelling with slight fatty degeneration was present. There was an increase in the interstitial connective tissue. In the pancreas and the liver arteriosclerosis

Fig. 5 (case 11).—Two arterioles and one small artery obtained from the kidney. The lumina of the three vessels are partially or totally occluded. Proliferation of the intima of the artery and degenerative changes in the wall of one arteriole, with hypertrophy of the media of the others, are to be noted.

narrowed the lumina of the smallest arteries and arterioles. There was a profound increase of the connective tissue in the spleen. The entire arterial tree was the seat of a well developed arteriosclerosis, causing occlusion of many of the finer arteries and arterioles. Sections from the pectoralis major showed no abnormal changes. The smallest arteries and arterioles of the lung were normal.

CASE 12.—J. R., a white woman, aged 50, entered the hospital on March 18, 1929, complaining of shortness of breath for the previous year. The blood pressure was 240 systolic and 120 diastolic. The radial and temporal arteries were small and wiry. There was no renal impairment. Heart failure was well developed. Ophthalmoscopic examination showed: edema of both disks, with many large petechial hemorrhages throughout the retina. The Wassermann reaction of the blood was negative. The patient appeared to be improving, when on March 22 she died suddenly.

Autopsy revealed the heart eccentrically hypertrophied to the left; it weighed 415 Gm. The valves were intact. There was atherosclerosis of the aorta. The coronaries were arteriosclerotic but not occluded. About 9 cm. above the area of the aortic valve there was a tear which penetrated between the intima and media. This dissecting aneurysm occupied the entire aortic wall down to the abdominal section. Both kidneys were smaller than normal, the right one weighing 105 Gm., and the left 95 Gm. The surface was finely granular. On cut surface the cortex was found to be thinned; the blood vessels were thickened and gaping. On microscopic examination, most glomeruli were found to be normal, while some were fibrosed; no necrotic loops were seen. In the epithelial cells of a few convoluted tubules were fatty deposits, none of which doubly refracted polarized light. The arterioles were universally narrowed, and in places they were occluded by the intimal thickening. Some of the arterioles showed fatty degeneration of their walls; the changes could be seen to involve all layers of the walls, occasionally with an aneurysmal dilatation of the vessels. The outstanding change in the arterioles and smallest arteries was a proliferation of the connective tissue of the intima. The elastic tissue was decidedly increased. Occasionally the media of the arterioles was thickened; usually it was atrophic. The changes in the arteries and arterioles of the liver were duplicated in the spleen and pancreas, where there was arteriosclerosis. Sections from the pectoralis major revealed hypertrophy of the media and adventitia; the intima was normal. No abnormal changes were found in the smallest arteries and arterioles of the lungs.

CASE 13.—A. M., a white laborer, aged 24, entered the hospital on July 26, 1927. His only complaint was headache. About one month prior to entrance he began to have pain in the back of the neck which slowly progressed into a headache that usually lasted all day and that disappeared at night. The past history was irrelevant except that the patient had had scarlet fever in childhood. He was well developed, and from all appearances seemed to be in good physical condition. The blood pressure was 264 systolic and 178 diastolic. No edema was present. The heart was in its normal position and the sounds were normal. Ophthalmoscopic examination revealed an exudative choroiditis; the veins were full and tortuous. The arteries were thin. Both disks were extensively swollen with edema. Fresh choroidal exudates were found around the fundi. In the macular area were old exudates with pigmentation. Petechial hemorrhages were present throughout. The Wassermann reaction of the blood was negative. The nitrogen content of the blood rose rapidly, especially toward the close of life. No dyspnea or edema developed. The course of the disease was followed until the patient died of renal insufficiency in December.

CASE 14.—M. K., a white woman, aged 47, entered the hospital on Feb. 2, 1929, complaining of headache, pain in the epigastrium and nocturia for the previous five months. No accurate data concerning the patient's past record could be obtained. The blood pressure was 230 systolic and 120 diastolic. The radial arteries were small, wiry and difficult to compress, but not tortuous, and the walls

were slightly thickened. Renal function was not impaired. Cardiac hypertrophy was moderate. Ophthalmoscopic examination showed the arteries to be thin and straight and the veins full. Many hemorrhagic areas were seen throughout both retinas; there was edema of both disks. The headaches became more severe; the patient lost 15 pounds (6.8 Kg.) in weight in two months, and her vision gradually failed. The Wassermann reaction of the blood was negative; no anemia was present. A biopsy of the pectoralis major muscle showed pronounced thickening of the media of the arterioles and smaller arteries; the lumen of all the arterioles were almost obliterated. There was a slight hyperplasia of the elastic tissue of the arteries, but the intima was practically normal.

CASE 15.—H. W., a white housewife, aged 38, was seen first on March 12, 1929. For the previous six months she had had edema of the ankles and face, profound dyspnea, severe headaches and visual disturbances with loss of vision at times. The symptoms became progressively worse. The family history was of interest in that the mother died of heart failure and the father of an apoplectic stroke. Of the four sisters living, two had blood pressures of over 180 systolic and 110 diastolic; of two brothers, one had a hypertension of 210 systolic and 125 diastolic. Urinalyses and an ophthalmoscopic examination of these six members of the family failed to show abnormalities. The patient had had hypertension for at least one year prior to the present complaint, and the urine had been pronounced normal on numerous occasions until two months prior to the present observation. The blood pressure was 240 systolic and 130 diastolic. The radials and temporals were not tortuous; the arterial walls were under great tension, but no more than slight thickening of the walls was found. The renal function was moderately reduced. The heart appeared to be normal. There was a pronounced edema of the legs, abdomen and face. Ophthalmoscopic examination showed that the arteries were tortuous; both disks were edematous, and many hemorrhages were seen in the peripheral zones. The Wassermann reaction of the blood was negative. The headaches became severe. The blood pressure persisted, and the patient gradually became worse. Permission to perform a biopsy on muscle was not granted.

CASE 16.—G. Z., a white girl, a factory worker, aged 19, was admitted to the hospital on July 5, 1925, with the complaint of severe headaches for one week. For four months she had suffered from nervousness, dyspnea and palpitation of the heart. The blood pressure was 256 systolic and 140 diastolic. Renal function was normal. The left border of the heart extended well outside its normal position; the apex beat was in the sixth intercostal space. A loud systolic murmur was found at the mitral, and a diastolic at the aortic, area. She was confined to bed because of weakness, dyspnea and headache. Ophthalmoscopic examination revealed pronounced edema of both disks, and many petechial hemorrhages in the retina of both eyes. The Wassermann reaction of the blood was negative. After two weeks in the hospital, the patient left against advice and has not been heard from since.

PRIMARY CARCINOMA OF THE LIVER*

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The comparative infrequency of primary carcinoma of the liver would seem to justify this report of nine such cases occurring at the Vancouver General Hospital during the years from 1920 to 1927, inclusive. During this period other cases occurred in which such a diagnosis was made, but these have been excluded from the present series either because of an incomplete autopsy or because the microscopic observations were open to question. The nine cases here reported are, we believe, undoubted instances of primary carcinoma of the liver.

At one time thought to be a common condition, true primary carcinoma of the liver is now known to be comparatively rare. Secondary involvement of the liver by metastasis from primary growths elsewhere, especially in the gastro-intestinal tract, is more common. No attempt will be made here to enter into any extensive discussion of the subject because of the excellent articles already available. In 1926, Counseller and McIndoe,[1] in a report of five cases from the Mayo Clinic, included an excellent discussion and bibliography to that date.

As far as the gross appearance is concerned, primary carcinoma of the liver is divided into massive, nodular and diffuse. Microscopically, these growths are of two types; hepatoma or true liver cell carcinoma and cholangioma or bile duct carcinoma. Six of these nine cases are true hepatomas and three are cholangiomas. Of these nine cases, eight were in Chinese and one in a white man. This considerably greater incidence of the disease in the Chinese seems worthy of some consideration. When this was first noted by one of us (G. F. S.) it was thought that the larger percentage of autopsies in our Oriental patients might account for this observation. This is not the case, however, for, while it is true that the percentage of autopsies in Chinese is practically twice that in white patients, at the Vancouver General Hospital, the much smaller number of Chinese admitted to that institution would only further emphasize the strikingly high incidence of primary carcinoma of the liver among these people.

* Submitted for publication, Aug. 21, 1929.

1. Counseller, V. S., and McIndoe, A. H.: Primary Carcinoma of the Liver, Arch. Int. Med. **37**:363 (March) 1926.

In table 1 we have summarized the number of deaths and the autopsies occurring at the Vancouver General Hospital in the white and in the Chinese patients.

During the eight years (1920 to 1927), 1,024 autopsies were performed, with the observation of nine cases of primary carcinoma of the liver, giving an incidence of 0.87 per cent, which we realize is high as compared with other series. Counseller and McIndoe, in reviewing a large series of reported cases, noted an incidence of 0.14 per cent in 42,276 autopsies. When our figures are analyzed and the white people and Chinese are separated, the incidence as far as the white man is concerned more nearly approximates this reported figure. In the 909 autopsies on white patients, primary carcinoma of the liver was found only once, giving an incidence of 0.11 per cent. In the

TABLE 1.—*Summary of Deaths and Autopsies at the Vancouver General Hospital*

Year	Total Deaths	White Deaths	White Autopsies		Chinese Deaths	Chinese Autopsies	
			Number	Percentage		Number	Percentage
1920	688	641	113	17.6	47	19	40.4
1921	508	468	121	21.3	30	12	40.0
1922	654	598	126	21.0	56	19	33.9
1923	552	513	124	24.1	39	10	25.6
1924	557	508	78	15.3	49	17	34.6
1925	663	616	95	15.4	47	13	27.6
1926	689	641	133	20.7	48	16	33.3
1927	738	714	119	16.6	24	9	37.5
	5,139	4,799	909	19.0 average	340	115	34.1 average

Total autopsies, 1,024.

Chinese series, among 115 autopsies the finding of eight such cases gives an incidence of 6.9 per cent. Because of this unusually high incidence, we have felt keenly the necessity of being absolutely certain of our observations before making any report. In order to check our results, we have submitted our material to Dr. William Boyd, professor of pathology at the University of Manitoba, who has reviewed the microscopic sections and has had the accompanying photomicrographs prepared. We have included in our report only those cases about which there appeared to be no doubt.

While it has been difficult to obtain accurate statistics from China as to disease incidence, such information as has been collected would indicate that there is an increased frequency of chronic diseases of the liver especially in southern China. The Chinese immigrants to British Columbia come from the southern province of Kwantung, and to make comparative figures of any value, it was necessary to secure data from that part of the country. There are no autopsy series available from Canton, but some interesting facts have been revealed. Dr. W. W.

Cadbury [2] of the Lingnan University, Canton, said that at a recent meeting of the China Medical Association in Shanghai, in the course of a discussion on cancer among the Chinese, the conclusion was reached that carcinoma of the breast is the most prevalent form, carcinoma of the penis and carcinoma of the cervix uteri, following in that order. This is of course for the whole of China and would indicate that for the whole country the incidence of carcinoma of the liver is not sufficiently increased to compare with those mentioned. Maxwell [3] made some interesting comparisons regarding the incidence of malignant disease in Chinese and on this continent. He compared a series of 1,133 cases of cancer as to location of the lesion with a series of 3,163 cases from Chicago (Hoffman). His observations agree with those just mentioned, that the commonest forms of cancer in China are those of the breast, penis and cervix in that order. He pointed out, however, that the carcinomas that are found in China are those that are looked for, and mentioned the fact that at one time he considered carcinoma of the uterus to be rare, but that, after a gynecological clinic was opened, he found this form of carcinoma common. It is of interest to note that these three forms of carcinoma, of the breast, penis and cervix, are external, and would be more easily discovered than the forms that could be disclosed only by careful autopsy. In Maxwell's series carcinoma of the liver and gallbladder was found in only 4 per cent as compared with 8 per cent in Hoffman's series. The absence of any certification as to the cause of death means that many obscure internal disorders will be overlooked. Maxwell mentioned that he knows that carcinoma of the liver is common in certain limited areas where infection with *Clonorchis* is common. Other observations also point to the fact that the incidence of primary carcinoma of the liver seems to coincide with that of infections with *Clonorchis sinensis*.

More pertinent figures for our purposes were obtained from Dr. Berglund,[4] at that time professor of medicine at the Peiping Union Medical College, who forwarded the following figures from Dr. J. C. Tull, government pathologist in Singapore. During 1926, among 1,312 autopsies there were 23 cases of nodular cirrhosis, 19 instances of syphilitic cirrhosis, 5 cases of biliary cirrhosis, and finally 6 cases of cirrhosis due to *Schistosoma*, making altogether 53 cases of cirrhosis. There were, further, 16 cases of primary carcinoma of the liver, contrasted with only 14 cases of primary carcinoma of the stomach. There is apparently a definitely increased incidence of chronic disease of the liver in southern China. Snijders [5] also mentioned that the most strik-

2. Cadbury, W. W.: Personal communication to the authors.
3. Maxwell, J. L.: Cancer Among Chinese, China M. J. **42**:69, 1928.
4. Berglund: Personal communication to the authors.
5. Snijders: Cancer in the Tropics, China M. J. **38**:303, 1924.

ing feature of his cases from Singapore is the high frequency of primary carcinoma of the liver among the Javanese as well as the Chinese (and mentioned that in 90 per cent of their cases the carcinoma occurs in cirrhotic livers). One reason for the high incidence of chronic disease of the liver is the increased occurrence of intestinal diseases, especially the high incidence of infection with parasites. *Schistosoma* produced a definite type of cirrhosis of the liver. Liver fluke, *Clonorchis sinensis,* is another common parasite in southern China and has been noted as the cause of cirrhosis and even carcinoma of the liver. Nauck and Liang [6] recently reported from Shanghai the case of a young Chinaman with primary carcinoma of the liver and an accompanying infection with *Clonorchis.* These authors reviewed the interesting etiologic relationship between helmiths and tumor growth, pointing out that nematode worms have been said to produce tumors in the stomachs of rats, that *Bilharzia* have produced malignant tumors of the bladder and that tumors of the liver have been attributed to *Schistosoma.* They also reviewed the other reported cases of primary carcinoma of the liver said to result from infection with *Clonorchis.* They pointed out that, while the increased incidence of chronic disease of the liver is not due alone to infection with *Clonorchis,* the common observation of chronic intestinal disease, including intestinal parasites, must be considered as an important factor in the production of these conditions of the liver. They concluded that the relatively high frequency of carcinoma of the liver in eastern Asia may be atributed to the prevalence of injuries to the liver resulting from the chronic inflammatory irritation leading to chronic hepatitis and cirrhosis of the liver. They also believe that infection with *Clonorchis* is one cause of primary carcinoma of the liver in China. Faust [7] studied the epidemiology of infection with *Clonorchis* and showed that it was never found in the north, occasionally occurred in central China, but was most common in the south, in the Province of Kwantung (where raw fish is eaten). As already mentioned, Chinese immigrants to British Columbia come almost entirely from Kwantung. These Chinese are commonly infected with liver fluke, though, it is rarely a cause of any demonstrable disability. In fact, clonorchiasis is not considered contagious, and aliens are not excluded because of the presence of the parasite unless the disease has affected the ability to earn a living.

One of the nine cases is presented here in detail as the patient was studied in the hospital for nearly four months before his death, and an antemortem diagnosis of primary carcinoma of the liver was made.

6. Nauck, E. G., and Liang, B.: Primärer Leberkrebs und Clonorchis Infektion, Arch. f. Schiffs- u. Tropen-Hyg. **32**:109 (March) 1928.

7. Faust, E. C.: Some Recent Aspects of the Epidemiology of Clonorchis Infection in China, China M. J. **39**:287, 1925.

The diagnosis was based largely on our previous frequent observation of this condition in Chinese patients. The other eight cases are presented briefly. It is to be regretted that the clinical details of these cases are so meager. Frequently, however, the patient was moribund or nearly so on admission and no history was obtainable.

REPORT OF CASES

CASE 1.—*History.*—Q. S., a Chinese laborer, aged 45, was admitted to Vancouver General Hospital on Oct. 22, 1926, complaining of swelling of the abdomen and legs and progressive weakness. The past history revealed nothing of importance. He had lived in Canada for twenty years.

In January, 1926, while working on a railroad near Prince Rupert, B. C., the patient became weak and felt unable to work. He consulted a local physician who could not determine the cause of his complaints. In July, he noticed that his abdomen was larger than usual, and he later noticed a rather tender lump in the right part of the epigastrium. He went to Vancouver in August, getting progressively weaker and steadily losing weight. His usual weight was 128 pounds (51.8 Kg.); the weight on admission was 110 pounds (49.9 Kg.).

Examination.—Examination revealed an emaciated, middle-aged Chinese man, unable to lie flat in bed because of shortness of breath. The heart was normal. The lungs were clear, with some dulness at the base of the right side. The abdomen was considerably enlarged by a tense collection of free fluid. After paracentesis of 70 ounces of chyliform ascitic fluid, a slightly tender nodular mass could be felt in the epigastrium and right hypochondrium. This mass was apparently the liver, although there was no general downward enlargement of that organ. Liver dulness extended upward in the right side of the chest to the level of the third rib. The liver was fixed, not coming down with inspiration or change of position. The spleen was not enlarged. No other masses or tenderness were present.

The results of the rectal examination were negative.

The nervous system was normal.

There was considerable edema of the legs and feet.

Laboratory Observations.—On repeated examination, the urine showed a trace of albumin and occasional hyaline casts. The Wassermann reaction of the blood was negative. The nonprotein nitrogen was 33 mg. per hundred cubic centimeters of whole blood. The blood count showed: red cells, 3,602,000; hemoglobin, 70 per cent; white cells, 5,500; polymorphonuclears, 76 per cent; lymphocytes, 24 per cent.

Roentgen examination showed the gastro-intestinal tract to be normal. There was no roentgen evidence of gastric carcinoma.

Fluoroscopic examination showed the right side of the diaphragm to be very much elevated, apparently as a result of an enlarged liver. Stereoroentgenograms of the lungs showed them to be clear. The right side of the diaphragm was elevated to the second rib.

Because of our previous observation of primary carcinoma of the liver in the Chinese, the condition of this patient was so diagnosed.

The patient remained in the hospital until his death on Feb. 13, 1927. The clinical course of his condition was typical of that associated with rapidly progressive cirrhosis of the liver. Six tappings were necessary to relieve the recurring ascites. In this case, merbaphen as a diuretic was remarkably effective and

had it not been for this drug more frequent drainage of the ascitic fluid would have been necessary. He was given 1 cc. of merbaphen intravenously every three days for nearly two months. Part of this time the merbaphen was accompanied by ammonium chloride. The acid salt did not appear to increase the effectiveness of the mercury diuretic—as even without ammonium chloride a definite diuresis occurred after each administration of the merbaphen. There was no change in renal function as a result of the long continued use of merbaphen as judged by urinalysis, phthalein excretion and nonprotein nitrogen of the blood.

Autopsy Report.—The body was that of a very emaciated, fairly well developed, Chinese man. The abdomen was considerably distended and apparently contained fluid. The lower part of the abdomen showed a number of small paracentesis wounds. Otherwise, external examination was negative. The usual midline incision from the manubrium to the symphysis was made and a great deal of somewhat chylous ascitic fluid poured forth from the abdominal cavity. The right lung was very firm in its lower half and seemed to be contiguous with the liver. The right lower lobe was completely compressed. The upper portions of the lung, that is, the middle and upper lobes, were slightly compressed, but still crepitant. The reason for the compression of the right lower lobe was seen to be due to an extremely large growth originating in the liver which had grown up through the diaphragm on the right and produced an upward displacement of the diaphragm and the lower lobe of the lung. It had not, however, invaded the lung tissue proper. The upper aspect of the growth was domelike and regular. On section it presented a somewhat lobulated grayish-white, firm, slightly bile-tinged carcinomatous appearance. The right lobe of the liver was generally involved, but a number of nodules were also present in the left lobe. A great deal of compression apparently had occurred on the portal system. The gallbladder, stomach, duodenum, prostate and intestinal tract did not show any evidence of new growth, which would account for the original focus with metastases to the liver. The left lung was relatively intact. The heart was removed without detaching it from the right lung and it was found that a projection of the growth, the size of a hen's egg, was present in the right auricle between the superior and inferior venae cavae. The abdominal viscera showed no particular evidence of any lesion beyond considerable passive venous congestion. Further examination of the body was negative. The diagnosis was primary carcinoma of the liver with extension through the right side of the diaphragm to the right pleural cavity and right auricle.

Chylous ascites was present.

Microscopic Observations.—Section through the tumor mass in the right pleural cavity and through the masses in the liver all showed a similar picture characterized by many cordlike aggregations of large, atypical, hyperchromatic cells, the nuclei of which showed frequent mitoses. They exhibited an unrestricted fashion of growth and were grouped about alveolar spaces as though attempting duct formation. Many of these spaces contained a homogeneous pinkish-staining, colloid-like material. A relatively dense cirrhosis prevailed throughout and many areas of degeneration and hemorrhagic extravasation were also evident.

Diagnosis.—The diagnosis was primary carcinoma of the liver (cholangioma type).

CASE 2.—Jung Yen, a Chinese laborer, aged 33, was admitted to the hospital on June 18, 1920. No history was obtainable. He presented marked edema of the feet, legs and abdomen. The liver was enlarged and nodular. The patient lived only one and one-half hours after admission to the hospital.

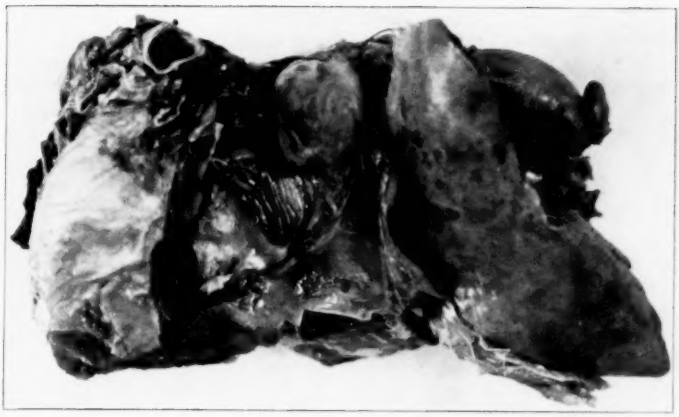

Fig. 1 (case 1).—The nodule in the right auricle. A portion of the liver, the right lung and the right auricle is shown. A mass of carcinomatous tissue, the size of a hen's egg, is shown projecting into the right auricular chamber. This is not metastatic but is a direct extension of the primary growth of the liver which had pushed through the diaphragm and lung tissue and finally the auricular wall.

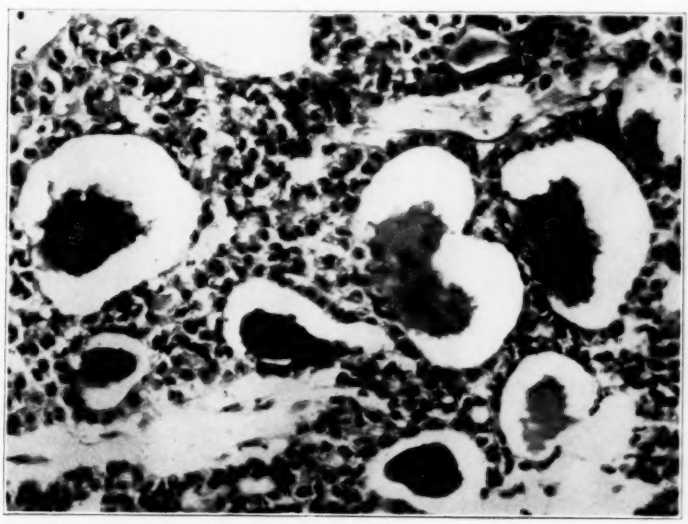

Fig. 2 (case 1).—Section of the tumor; × 175. "The tumor cells, although in places arranged diffusely, are for the most part grouped around alveolar spaces —the cells are fairly uniform in size. I should be inclined to class this as a bile duct carcinoma" (Dr. William Boyd).

Autopsy Report.—There was marked edema of the lower extremities and ascites. The liver weighed 6,050 Gm. There were grayish-white nodules of varying size, from 1 to 6 cm. in diameter, almost all in the right lobe. The intervening liver tissue was grossly cirrhotic. Metastatic nodules were present in both lungs. No evidence of other primary growth was revealed on further examination.

Microscopic Observations.—In this tumor the cells were not as large as those seen in several of the other tumors of this series. They were slightly pleomorphic, and the nuclei were hyperchromatic, pyknotic and mitotic. The cells were arranged in solid, relatively small aggregations with no attempt at acinar or duct formation, and in one area a definite tumor embolus was seen in a large vein. A well defined cirrhosis was present throughout.

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

CASE 3.—Yee Mah, a Chinese laborer, aged 45, was admitted to the hospital on March 11, 1921. The past history revealed nothing significant. For fourteen months he had suffered from loss of weight and pain in the upper part of the abdomen, with occasional attacks of fever.

The patient was emaciated, with definite ascites and edema of the feet and legs. The liver was enlarged. He died on April 4.

Autopsy Report.—There was edema of the lower extremities. The peritoneal cavity was filled with bloody fluid. The liver weighed 4,970 Gm. The right lobe almost completely replaced by large, grayish-white tumor masses, one, superficially placed, being extremely degenerated and hemorrhagic, apparently the source of the intraperitoneal hemorrhage. The left lobe was also studded with smaller nodules, many of which were bile stained, the intervening liver substance being cirrhotic. Metastatic nodules were found in the lungs, omentum and brain. No other primary growth was found on further examination of the body.

Microscopic Observations.—Sections through the tumor tissue showed it to consist of an aggregation of large, atypical, pleomorphic, hyperchromatic cells, many of which were extremely large with multinucleation and mitoses. In some areas the cells were arranged in fairly compact masses, in others more loosely arranged, but on the whole the stroma was sparse and fairly general degeneration was apparent throughout. Definite periportal cirrhosis was in evidence.

Diagnosis.—The diagnosis was primary carcinoma of the liver with cirrhosis (hepatoma type).

CASE 4.—Gee Yuen, a Chinese laborer, aged 57, was admitted to the hospital on Jan. 17, 1921. He presented swelling of the feet and abdomen, weakness and loss of weight for one month. Ascites and edema of the feet were present. He died on January 24.

Autopsy Report.—Relatively little of note was found on external examination. There was no edema of the extremities or ascites. The peritoneal cavity was filled with clotted and fluid blood. The omentum was adherent apparently by recent adhesions to a mass in the inferior aspect of the right lobe of the liver in which a deep hemorrhagic split was present, evidently the source of the hemorrhage. The liver weighed 3,060 Gm. It had been converted into a rather sclerotic, yellowish-white mass with relatively little normal liver tissue present, with areas of necrosis throughout. Finger-like processes of tumor tissue were found protruding into the inferior vena cava. No metastases were found in the lungs, etc., and there was no evidence of other primary growth elsewhere in the body.

Microscopic Observations.—The cells were large, fairly uniform, hyperchromatic and atypical; the nuclear material was especially dense but the cells generally showed none of the giant-like forms seen in many of the hepatoma types. They were arranged about definite, variously sized, ductlike spaces while in many areas definite tumor emboli were seen within vascular channels. Degenerative and inflammatory changes were in evidence with a definite but relatively fine cirrhosis throughout.

Diagnosis.—The diagnosis was primary carcinoma of the liver (cholangioma type).

Case 5.—Lim Hong Kit, a Chinese laborer, aged 47, was admitted to the hospital on June 24, 1922. No history was obtainable. He complained of ascites and edema of the legs. He died on June 25.

Autopsy Report.—There was some edema of the lower extremities. The peritoneal cavity was filled with serosanguineous fluid. The liver weighed 2,400 Gm. and was markedly cirrhotic in appearance, with many smaller and larger grayish-white nodules scattered throughout, chiefly in the right lobe. In one area, a process of tumor tissue protruded into the right portal vein. Several grossly involved perigastric lymph glands were present. There was no evidence of further metastases or other primary growth on further examination.

Microscopic Observations.—The cells were pleomorphic, generally pale staining and arranged in solid sheets surrounding spaces which were evidently vascular sinuses lined by elongated endothelial cells apparently of the Kupffer type. In other areas, aggregations of disimilar cells were seen which were of relatively enormous size, pale and with multinucleation into many bizarre formations. Dense fibrotic bands surrounded these areas while in the former areas definite but finer cirrhosis was evident.

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

Case 6.—Hong Chip, a Chinese laborer, aged 21, was admitted to the hospital on Nov. 5, 1922. Six days before admission he noted anorexia, headache and increasing vomiting. He was in coma at the time of admission. He died two days later.

Ascites were present; the liver was palpable. There was no edema of the feet.

Autopsy Report.—There was no edema or ascites. The liver weighed 1,950 Gm. A single, large, grayish-white mass almost completely replaced the right lobe of the liver with a few smaller discrete nodules surrounding it. No metastases were found and no other primary growth was revealed on further examination of the body.

Microscopic Observations.—The tumor cells were uniform in size, rather small and for the most part surrounded gland or ductlike spaces, many of which were very elongated. Mitotic figures were numerous, but none of the very large cells were seen. A moderate amount of coarse cirrhosis was present throughout.

Diagnosis.—The diagnosis was primary carcinoma of the liver (cholangioma type).

Case 7.—Lim Lap Fon, a Chinese laborer, aged 53, was admitted to the hospital on May 15, 1923. Extreme emaciation was evident. There was no edema of the extremities. The liver was slightly enlarged. There were no ascites. The patient died on May 26.

Autopsy Report.—External examination gave negative results. There was no ascites or edema. The liver weighed 2,000 Gm. and was studded with grayish-

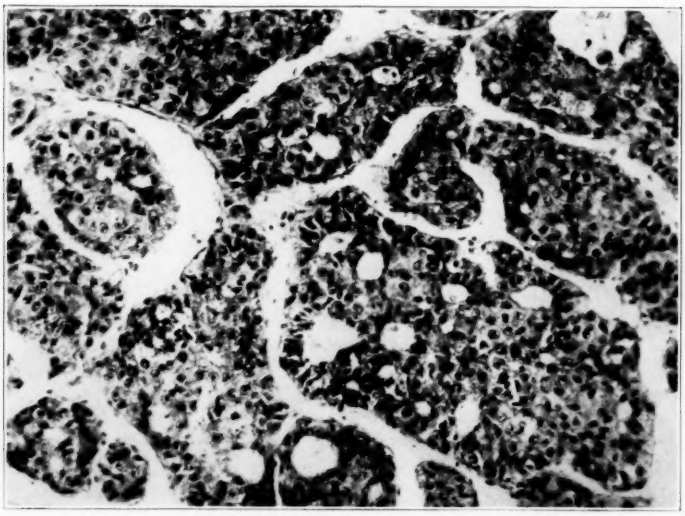

Fig. 3 (case 4).—Section of the tumor; × 125. "The photomicrograph shows very clearly the early picture of bile duct carcinoma, with a certain arrangement of cells around ductlike spaces" (Dr. William Boyd).

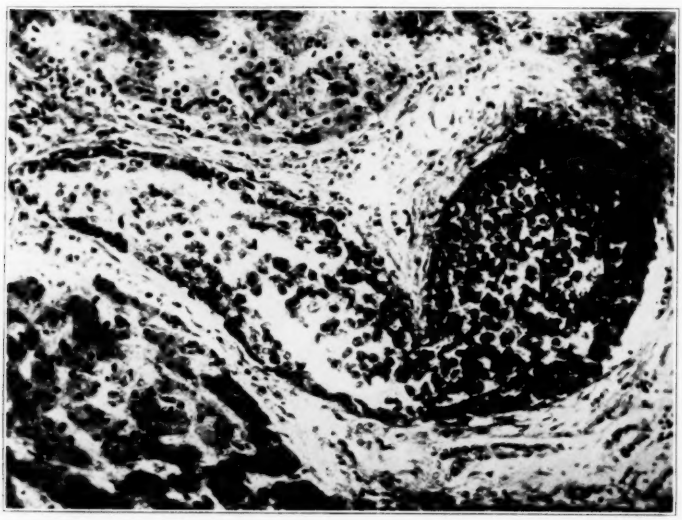

Fig. 4 (case 4).—Tumor embolus; × 125. Extension of the tumor.

white nodules from 2 mm. to 2 cm. in diameter throughout both lobes. A few smaller, similar nodules were present in the spleen. Several metastatic nodules were found in three of the left ribs. No other primary growth was found on examination of the remainder of the body.

Microscopic Observations.—Throughout these sections many cords and columns of pleomorphic cells of liver type were seen. Many of them were extremely large, with correspondingly large nuclei in which mitotic figures were frequent. Interspersed throughout one saw well defined bands of fibrous tissue of cirrhotic type in which fairly numerous but well developed biliary ducts were present.

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

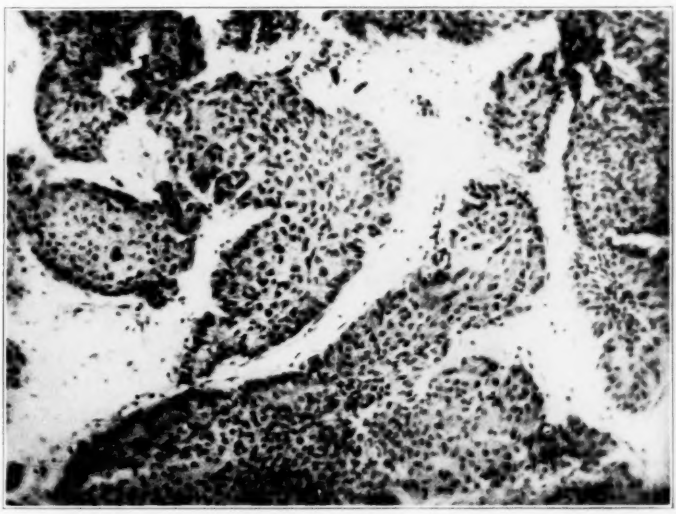

Fig. 5 (case 6).—Section of the tumor; × 125. "Most of the section is composed of sheets of cells resembling liver cells, the sheets being separated by large spaces, probably blood spaces. These spaces are lined by very distinct endothelial cells which apparently represent unusually distinct Kupffer's cells. In addition to the sheets, there are a few areas quite different in appearance, composed of huge, pale, multinucleated cells, similar to those seen in other primary liver cell tumors. The latter areas are surrounded by dense fibrous tissue" (Dr. William Boyd).

Case 8.—McM., a white laborer, aged 76 years, was admitted to the hospital on July 12, 1926. He had had weakness for two years. The edema of the feet, legs and abdomen was getting gradually worse. He was comatose at the time of admission. He died on July 13.

Autopsy Report.—There was edema of the lower extremities. Serosanguineous fluid was present in the peritoneal cavity and in both pleural cavities. The liver weighed 2,500 Gm. and was studded throughout with many grayish-white, bile

stained nodules, while a larger superficial mass on the superior surface of the right lobe was adherent to the hepatic flexure of the colon but did not extend into the lumen. Metastatic nodules were also present in the lungs. No other primary growth was found on further examination of the body.

Microscopic Observations.—The picture presented in the sections from this tumor was practically identical with that seen in case 7, with the exception of an almost complete absence of cirrhotic changes. This would seem to be rather of interest owing to the fact that it is from the only white man in our series and the only patient showing no cirrhosis.

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

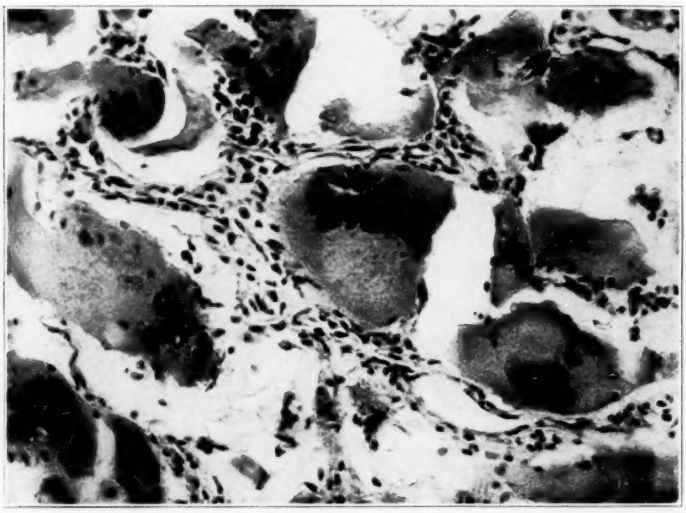

Fig. 6 (case 6).—Section of the tumor, showing large multinucleated cells surrounded by dense fibrous tissue; × 200.

CASE 9.—Leung Ling, a Chinese laborer, aged 35, was admitted to the emergency ward in an unconscious state on Sept. 5, 1927, and died within a few minutes after admission.

Autopsy Record.—The body was that of a well developed and nourished Chinese man. Nothing remarkable was apparent on external examination. The peritoneal cavity was completely filled with clotted and fluid blood, the source of which was found at the margin of the lower portion of the right lobe of the liver where a large degenerated carcinomatous mass, 8 by 6 cm., had eroded a large blood vessel, the thrombosed end of which was apparent. The liver was small, weighing only 1,090 Gm. It was markedly cirrhotic. In the right lobe many grayish-white nodules, varying in size from that of a filbert to that previously noted, were seen, all more or less degenerated in appearance. The left lobe was free from nodules. A large tumor embolus was present in the first portion

of the inferior vena cava. No gross metastases were found, and further examination of the body revealed no other primary growth.

Microscopic Observations.—Sections through the liver showed the presence of many aggregations of atypical liver cells, some of which appeared to be from eight to ten times the size of the normal cells, irregular in shape, with large, single or multiple hyperchromatic nuclei frequently showing mitosis. No attempt at acinar or duct formation was apparent although in a few areas the cells were arranged in solid cylindric formations frequently showing considerable central degeneration. Extensive cirrhosis was present throughout with dense bands of fibrous tissue surrounding masses of these atypical cells. No tumor emboli were evident in the sections.

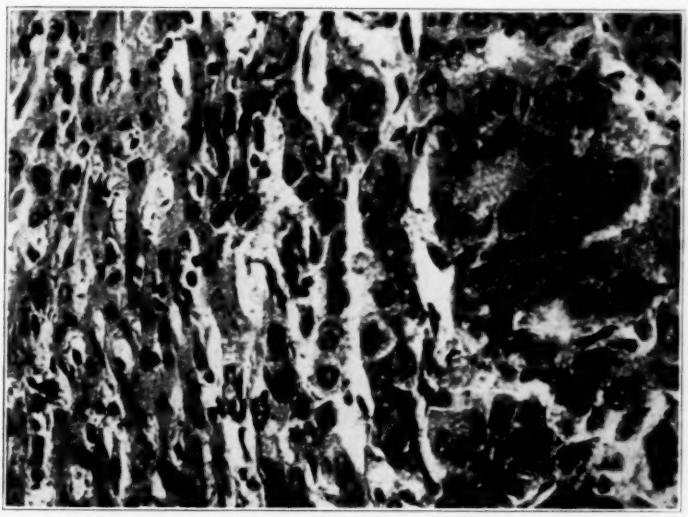

Fig. 7 (case 7).—Section of the tumor; × 300. "Scattered throughout the section of the liver are numerous large tumor masses, which are composed of irregular cords of cells the general structure and arrangement of which resemble that of normal liver tissue. Many of the cells are very large and possess huge nuclei. There are numerous mitotic figures. In some places the tumor cells can be seen to arise from the liver cells. There is a well marked cirrhosis and in the cirrhotic material are numerous new bile ducts. These do not show any evidence of malignant neoplasia. This is evidently a hepatoma with cirrhosis" (Dr. William Boyd).

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

COMMENT

Sex and Age.—All nine cases occurred in males. The fact that eight Chinese patients were men may or may not be of some significance. The much smaller number of Chinese women living in British Columbia

would account in part for this sex incidence. The definite preponderance of males suggests some environmental factor.

The average age in this series was 45.6 years with extremes of from 21 to 76 years.

Symptoms.—There are no symptoms pathognomonic of this condition. The clinical picture presented is that of a rapidly progressing cirrhosis of the liver. It is not possible to diagnose with accuracy primary carcinoma of the liver without a complete autopsy. The common symptoms are weakness, loss of weight, ascites, swelling of the feet and legs and gastro-intestinal disturbances; vomiting or diarrhea may occur. Jaundice is not a constant occurrence. One feature which we believe is rather common is the fact that the liver becomes fixed, and frequently enlarges upward to a greater extent than downward. The fixation is apt to occur early, and the upward enlargement is favored by the fact that the diaphragm and right lung present less resistance than the fluid-filled peritoneal cavity. Because of the fixation and upward enlargement of the liver, the fact of enlargement may be

TABLE 2.—*Age Incidence*

Decade	Chinese	White
21 to 30	1	0
31 to 40	2	0
41 to 50	3	0
51 to 60	2	0
61 to 70	0	0
71 to 80	0	1

overlooked since it is customary to estimate liver enlargement by the degrees of the extension of its lower boarder below the costal margin. The result of fixation and upward enlargement was clearly shown in case 1 in which roentgen examination showed the dome of the liver up to the second rib.

Pathology.—As mentioned before, primary carcinoma of the liver may be divided into two types on the basis of the cellular pathologic changes: (1) hepatoma, a true liver cell tumor, and (2) cholangioma, a bile duct tumor. The histologic features of these two types of carcinoma are described in connection with the cases here presented and in the description of the accompanying photomicrographs. Further discussion of these observations is unnecessary. In this series, there were six hepatomas and three cholangiomas.

The relation of cirrhosis to primary carcinoma of the liver is definitely established. Counseller and McIndoe went so far as to question the diagnosis of a primary carcinoma of the liver in the absence of a definite cirrhosis. The cirrhosis may be either portal or biliary and is probably a precursor of the carcinoma. In cirrhosis, a degeneration of the liver cells and bile ducts occurs followed by some evidence of

regeneration or attempts at regeneration, which may result in the disorderly growth which characterizes these carcinomas. Eggel [8] found cirrhosis in 85 per cent of hepatomas and 50 per cent of cholangiomas. In our series, cirrhosis was present in all three of the cholangiomas and in five of the six hepatomas, the exception being in the only white patient in the series.

Metastases appear to occur entirely by the blood stream. The hepatomas invade the capillaries, and gross tumor emboli are frequently seen in these cases in portal vein radicals and in the inferior vena cava. The cholangiomas are said to metastasize earlier and more frequently than the hepatomas. In this series, however, metastases were more frequent among the hepatomas, occurring in five of the six cases, and being found in only one of the three cholangiomas. The lungs were involved in four cases, the ribs and spleen in one case, the mesenteric and perigastric glands in one and the brain in one. The nodule shown in figure 2 is not a metastasis but rather an extension of the tumor substance into the cavity of the right auricle.

Of some interest is the fact that three of our patients died suddenly as a result of extensive intraperitoneal hemorrhage caused by erosion of a large vessel by a tumor nodule. Similar observations have been reported by Karsner.[9]

While nothing has been added to our knowledge of primary carcinoma of the liver by this contribution, it seemed worthy of record: (1) because of the rather large number of cases of a comparatively rare condition and (2) because of the high incidence in the Chinese. This increased incidence in the Chinese in our series is, we believe, a result of the fact that these immigrants come from Kwantung, a province in China where chronic disease of the liver and primary carcinoma of the liver are of more frequent occurrence than in other parts of China. Infection with *Clonorchis* may have been the exciting factor in the production of some of these primary carcinomas, while others may have resulted from chronic irritation of the liver due to other causes (hepatitis with resulting cirrhosis). While the actual parasites were not found in any of our cases, the infection with *Clonorchis sinensis* is after all only the exciting factor, the parasites setting up a chronic irritation resulting in a cirrhosis and in some cases in primary carcinoma.

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9. Karsner, H. T.: A Clinicopathological Study of Primary Carcinoma of the Liver, Arch. Int. Med. **8**:238 (Aug.) 1911.

CONCLUSIONS

A series of nine cases of primary carcinoma of the liver is presented, eight of which occurred in Chinese.

These Chinese came entirely from Kwantung, a southern province of China, where liver fluke, *Clonorchis sinensis*, is common, and where chronic diseases of the liver frequently occur.

CHRONIC ARTHRITIS

BACTERIOLOGY OF AFFECTED TISSUES *

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AND
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In an attempt to explain the etiology of nonspecific chronic arthritis, there have emerged widely conflicting opinions based, at times, entirely on clinical or laboratory observations. But in view of the lack of definitive conclusions, it seems desirable to correlate our laboratory observations with clinical observations to determine what light may be shed on this rather perplexing problem.

The opinions of most writers in recent years have begun to lean toward the primarily infectious nature of chronic arthritis. Although, admittedly, the modus operandi of such infections has not been clarified, a great amount of reliable data has already accumulated in support of the infectious theory. Clinically, the frequent occurrence of arthritis in the course of acute infections such as scarlet fever, typhoid fever, malta fever, ulcerative colitis, and so forth, is well recognized. The extensive researches of Rosenow [1] and his co-workers [2] have emphasized the rôle of focal infection in arthritis and of the elective localizing tendencies of bacteria isolated from foci of patients with arthritis. The observations of Billings [3] pointed in the same direction. Indeed, the observations of many clinicians have led them to a conception of arthritis

* Submitted for publication, Dec. 1, 1929.

* Work done in the Division of Medicine and Division of Experimental Bacteriology under the direction of L. G. Rowntree, P. S. Hench and E. C. Rosenow.

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2. Meisser, J. G., and Brock, Sam: A Clinical and Experimental Study in Chronic Arthritis, J. Am. Dent. A. **10**:1100, 1923. Nakamura, T.: A Study of Focal Infection and Elective Localization in Ulcer of the Stomach and in Arthritis, Ann. Surg. **79**:29, 1924. Nickel, A. C.: The Localization in Animals of Bacteria Isolated from Foci of Infection, J. A. M. A. **87**:1117 (Oct. 2) 1926.

3. Billings, Frank: Chronic Focal Infection as a Causative Factor in Chronic Arthritis, J. A. M. A. **61**:819 (Sept. 13) 1913; Focal Infection: Its Broader Application in the Etiology of General Disease, ibid. **63**:899 (Sept. 12) 1914.

as an insidious infectious process, producing the most striking changes in the joints, but having as a counterpart such phenomena as debility, at times generalized lymphadenopathy, splenomegaly and anemia, and low grade fever, all indicative of a low grade infectious process. Hench [4] aptly described these phenomena as the systemic manifestations of the disease. Attempts to substantiate the infectious nature of chronic arthritis by bacteriologic cultures of material from joints, however, have not always proved successful. Cultures from supposedly "infectious arthritis" have frequently been found sterile, and this has been adduced as proof of the noninfectious nature of the process.

In view of the relationship of the reticulo-endothelial system to bacterial infections and the manifestations of its involvement in many cases of so-called infectious arthritis, and because of its close anatomic relationship to the joint, it seemed to us that a bacteriologic study of the epiphyseal marrow underlying affected joints might yield cultures of the offending organisms more consistently than the synovial membrane or synovial fluid, to which most of the attention has been directed in the past. Accordingly, we conducted a bacteriologic study on material obtained from the joints of patients who came to operation in the Section on Orthopedic Surgery at the Mayo Clinic. Although we were primarily interested in cultures of the marrow, we also attempted cultures of excised synovial membrane, joint fluid, cartilage and the periarticular capsule.

REVIEW OF THE LITERATURE

Schüller,[5] in 1892, described a dumbbell-shaped bacillus which he observed in stained sections of synovial membrane from cases which he designated "polyarthritis chronica villosa." In a subsequent communication,[6] he described this organism as a gram-positive, short, plump rod showing polar granulation. Although as a rule the organisms presented the characteristic dumbbell shape, in exceptional cases they were very short with only a slight compression in the middle, so that they resembled, somewhat, diplococci. By 1906, Schüller [7] was able to demonstrate the presence of this organism either in the joint fluid or in the synovial membrane in 150 of 230 cases of chronic villous polyarthritis.

4. Hench, P. S.: The Systemic Nature of Chronic Infectious Arthritis, Atlantic M. J. **28**:425, 1925.

5. Schüller, Max: Chirurgische Mittheilungen über die chronisch rheumatischen Gelenkentzündungen, Verhandl. d. deutsch. Gesellsch. f. Chir. **21**:406, 1892.

6. Schüller, Max: Untersuchungen über die Aetiologie der sogenannten chronisch rheumatischen Gelenkentzündungen, Berl. klin. Wchnschr. **30**:865, 1893.

7. Schüller, Max: The Relations of Chronic Villous Polyarthritis to the Dumb-Bell Shaped Bacilli, Am. J. M. Sc. **132**:231, 1906.

Bannatyne, Wohlman and Blaxall,[8] in 1896, demonstrated the presence of a minute gram-negative bacillus, exhibiting polar staining, in the synovial fluid of eighteen cases of "rheumatoid arthritis."

In the few sections Bannatyne[9] was able to obtain, he found the same organism as that found by Blaxall in the cartilage, synovial membrane and periarticular tissues.

Poynton and Paine[10] obtained a diplococcus from the synovial membrane in one case of arthritis and produced arthritis in two rabbits by the injection of this organism.

Fayerweather[11] found three types of bacteria in four positive cultures from joints. Three of these were from cases of chronic periarticular arthritis corresponding in type to Schüller's villous polyarthritis.

In 1922, Billings, Coleman and Hibbs[12] reported positive results in six of fourteen cultures of joints. Of these, five cultures showed green-producing streptococci and one culture showed hemolytic and nonhemolytic streptococci.

In the course of a bacteriologic investigation of chronic arthritis, Mutch[13] obtained a pure culture of *Bacillus fallax* in one case.

Crowe[14] favored the opinion that so-called osteo-arthritis is caused primarily by streptococci, whereas in rheumatoid arthritis a strain of *Staphylococcus albus* is the primary cause. He labeled this organism *Micrococcus deformans*, and isolated it in several instances from the bone and pannus in cases of affected joints. He expressed the belief that streptococci found in rheumatoid arthritis represent secondary invaders.

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8. Bannatyne, G. A.; Wohlman, A. S., and Blaxall, F. R.: Rheumatoid Arthritis: Clinical History, Etiology and Pathology with a Report on Its Bacteriology, Lancet **1**:1120, 1896.

9. Bannatyne, G. A., quoted by Llewellyn-Jones, R.: Arthritis Deformans: Comprising Rheumatoid Arthritis, Osteo-Arthritis and Spondylitis Deformans, New York, William Wood & Company, 1909, p. 59.

10. Poynton, F. J., and Paine, Alexander: An Experimental Production of the Osteo-Arthritic Type of Rheumatoid Arthritis, Tr. Path. Soc. London **53**: 221, 1902.

11. Fayerweather, Roades: Infectious Arthritis: A Bacteriological Contribution to the Differentiation of the "Rheumatic" Affections, Am. J. M. Sc. **130**: 1051, 1905.

12. Billings, Frank; Coleman, G. H., and Hibbs, W. S.: Chronic Infectious Arthritis, J. A. M. A. **78**:1097 (April 15) 1922.

13. Mutch, N.: An Intestinal Anaerobe and Chronic Arthritis, M. J. & Rec. **126**:563, 1927.

14. Crowe, H. W.: Bacteriology and Surgery of Chronic Arthritis and Rheumatism with End Results of Treatment, London, Oxford Medical Publications, 1927, p. 76.

Rosenow[15] cultured one or more lymph nodes which drained inflamed joints in fifty-four cases of arthritis deformans, and isolated organisms as follows: modified *Streptococcus viridans* thirty-two times; staphylococci five times; *Bacillus mucosus* three times; gonococci once; *Micrococcus catarrhalis* once; Welch's bacillus in fourteen cases, and diphtheroids in five cases. In some cases of deforming arthritis, he isolated the same organisms simultaneously from the fluid or capsule of the joints and the excised lymph node.

Among recent reports is that of Forkner, Shands and Poston.[16] They obtained cultures in the fluid from the joint in fourteen of sixty-three cases studied. In eleven of these, the organism was *Streptococcus viridans,* in two, gonococci and in one, *Staphylococcus aureus.* In the twenty-one cases in which regional lymph nodes were cultured, the culture was positive in ten; in nine cultures the organism was *Streptococcus viridans,* and in one culture it was the gonococcus.

Cecil, Nicholls and Stainsby[17] found an atypical *Streptococcus viridans* in the curetted material from the head of the femur in two cases of chronic arthritis. Cultures of the synovial membrane and lymph nodes in six cases were sterile. They were also successful in obtaining an atypical streptococcus from the blood in a rather high percentage of the cases studied.

In contrast to these observations, Crawford and Malim,[18] who cultured the fluid from the joints in forty-eight cases of chronic arthritis, found the majority of the cultures to be sterile, and in a few cases from which organisms were cultured it was thought they were the results of accidental contamination.

Similarly, Richards,[19] who attempted cultures of the joints in fifty-four cases of chronic synovitis, obtained *Streptococcus viridans* in only four cases. It is significant that these cultures were taken during an acute exacerbation, and an attempt was made to obtain fluid from the inflamed periarticular tissues as well as from the cavity of the joint.

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15. Rosenow (footnote 1, first reference).

16. Forkner, C. E.; Shands, A. R., Jr., and Poston, M. A.: Synovial Fluid in Chronic Arthritis: Bacteriology and Cytology, Arch. Int. Med. **42**:675 (Nov.) 1928.

17. Cecil, R. L.; Nicholls, Edith E., and Stainsby, W. J.: Bacteriology of Blood and Joints in Chronic Infectious Arthritis, Proc. Soc. Exper. Biol. & Med. **26**:6, 1928.

18. Crawford and Malim, quoted by Llewellyn-Jones, R.: Arthritis Deformans; Rheumatoid Arthritis, Osteo-Arthritis and Spondylitis Deformans, New York, William Wood & Company, 1909, p. 62.

19. Richards, J. H.: Bacteriologic Studies in Chronic Arthritis and Chorea, J. Bact. **5**:511, 1920.

In 1923, Swett,[20] studied the synovial membrane obtained from fifteen synovectomies on eight patients suffering from chronic arthritis. These cultures were all sterile. In only one stained specimen were micro-organisms seen. Similar observations were reported by Kinsella [21] in 100 cases of chronic arthritis: "None of these gave positive cultures as far as the joints were concerned."

The absence of any unanimity of opinion with regard to bacteriologic observations in arthritis is striking; we shall later comment on some plausible explanations for it.

MATERIAL FOR STUDY

The material used for this study came from two main groups of cases. The first comprised a series of cases in which clinical evidence of nonspecific chronic arthritis was presented. Most of these cases presented the characteristic picture of swelling in many joints, deformity and ankylosis. Clinically and at operation, these were diagnosed "chronic infectious arthritis." This corresponds to the "rheumatoid arthritis" of the British school, which is called "proliferative arthritis" according to the classification of Nicholls and Richardson, and "atrophic arthritis" by Goldthwait. The diagnosis of chronic synovitis was made in those cases in which only thickening of the synovia and periarticular structures was presented, usually with effusion of fluid into the cavity of the joint, but without demonstrable destruction of cartilage. One patient in this group, whose leg had been amputated for arteriosclerotic gangrene, had incidental arthritis of the knee with destruction of the cartilage of the femur and tibia and slight thickening of the synovial membrane. This case was of the type often designated "osteo-arthritis." The material became available for study when these patients came for reconstructive orthopedic operations, such as arthroplasty, arthrodesis and synovectomy. In some cases in which it was deemed advisable to aspirate large amounts of fluid, a section of the synovia was usually excised for pathologic and bacteriologic study.

The duration of the arthritis from the onset of symptoms was a matter of years in most cases. Thus, with the exception of four cases, in which the duration was three weeks, five months, eight months and ten months, respectively, the duration of the disease was from one to twenty years; the average was six and three-tenths years.

When pathologic examination of the excised tissues and the fluid was performed, it confirmed the clinical diagnosis of the nonspecific inflammatory nature of the arthritis.

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20. **Swett, P. P.**: Synovectomy in Chronic Arthritis, J. Bone & Joint Surg. **5**:110, 1923.

21. Kinsella, R. A.: Chronic Infectious Arthritis, J. A. M. A. **80**:671 (March 10) 1923.

The second group of patients was used as controls, since this group afforded material from noninfected joints and from joints which clinically or pathologically were proved to be cases of tuberculous arthritis. The group also included two other cases: one case of old chronic osteomyelitis of the humerus with secondary involvement of the elbow, producing ankylosis, and the other, a case of old septic arthritis of the knee which had healed with resulting ankylosis.

TECHNIC

The tissues were excised at operation under aseptic precautions and were immediately taken to the laboratory for culture. Pieces of epiphyseal marrow and bone, synovial membrane, cartilage and periarticular capsule were embedded in tall tubes of dextrose-brain agar or planted in tubes of dextrose-brain broth. The reaction of the medium was adjusted to a hydrogen ion concentration of from 7.2 to 7.4. A part of the tissue, to which was added a small amount of sterile white sand and 5 cc. of dextrose-brain broth, was emulsified in a mortar under aseptic precautions. Tall tubes of dextrose-brain broth and dextrose-brain agar were then inoculated with varying amounts of these emulsions, several tubes being used as a rule for each specimen of tissue. When small quantities of synovial fluid were obtained, the entire amount of from 5 to 8 cc. was planted directly in dextrose-brain agar and dextrose-brain broth. When larger quantities were available, the fluid was centrifugated and the sediment was planted. The cultures were examined for growth at frequent intervals, over a period of from twenty-four hours to ninety days.

RESULTS

Fifteen of the twenty-five cases comprising the group of chronic infectious arthritis were classified clinically as chronic infectious arthritis, nine as chronic synovitis and one as osteo-arthritis associated with arteriosclerotic gangrene. Thirteen specimens of epiphyseal marrow and bone underlying the cartilage of the affected joints in the cases of chronic infectious arthritis were cultured. Six of these cultures were positive: two yielded indifferent streptococci; one a green-producing streptococcus, and three, diphtheroids. The remainder were sterile with the exception of an occasional tube in some series of cultures which showed a growth of *Staphylococcus albus*, apparently the result of accidental contamination. Two of eight specimens of synovial membrane obtained from the same patients were positive, one organism being a green-producing streptococcus and the other a diphtheroid. Six specimens of synovial fluid did not yield growth. One of the five specimens of synovial membrane obtained from the nine cases of chronic synovitis yielded a growth of diphtheroids. The eight specimens of synovial fluid from these patients were sterile. Two specimens of epiphyseal marrow were obtained from the knee of the patient with osteo-arthritis. One of these yielded a pure culture of indifferent streptococci. In the synovial membrane from the same joint slightly

green-producing and indifferent streptococci were found. One of the two specimens of cartilage from this joint yielded a culture of green-producing streptococci and *Staphylococcus albus*.

Thus, of the total of fifteen specimens of epiphyseal marrow and bone from various types of chronic infectious arthritis, seven were positive. Three of the organisms were indifferent streptococci, one was a green-producing streptococcus and three were diphtheroids. Of fourteen specimens of synovial membrane, four were positive; in two cultures the organisms were green-producing and indifferent streptococci, and in two, diphtheroids. One of the two specimens of cartilage yielded green-producing streptococci and *Staphylococcus albus*. The fourteen specimens of synovial fluid obtained from all these cases were sterile, except for contamination with gram-positive bacilli in two cases. In a few other instances (five specimens of epiphyseal marrow, and three specimens of synovial membrane), an occasional tube showed *Staphylococcus albus* or gram-positive bacilli which were probably the result of accidental contamination.

In contrast with these data are the results of cultures from the series of cases used as controls. Forty specimens of tissue were available for this purpose. Twenty-one of these specimens were from noninfected joints. Among these were cases of internal derangement of the knee joint, simple intracapsular fractures and old poliomyelitis in which arthrodesis was performed. Fourteen specimens were from proved cases of tuberculous arthritis; one specimen was from a case of old chronic osteomyelitis with secondary involvement of the joint, and four specimens were from a case of old septic arthritis of the knee. These forty specimens of tissue comprised epiphyseal marrow and bone, synovial membrane, synovial fluid, cartilage and the periarticular capsule. Ten of the seventeen cultures that were positive yielded *Staphylococcus albus*, two gram-positive bacilli, two micrococci, two gram-positive bacilli and *Staphylococcus albus* and one a diphtheroid. Some of these organisms were obviously the result of contamination, but it is probable that in other instances the organisms represented secondary invaders in diseased tissue. The significant fact is that in none of these forty control specimens did we find any cultures of streptococci, and the culture of diphtheroids came from the specimen of epiphyseal marrow from the case of septic arthritis secondary to old chronic osteomyelitis.

The streptococci that were obtained from the arthritic tissues were all streptococci in short chains (figs. 1 and 2). On blood agar none produced hemolysis. The predominating tendency was not to produce pigmentation, but in some instances the primary cultures either showed a slight greenish pigmentation or were definitely of the green-producing variety. Morphologically, the diphtheroids appeared to be midway between true diphtheroids and very short chains of fine streptococci.

Fig. 1.—Dextrose-brain broth culture of short-chained (indifferent) streptococci from epiphyseal marrow in chronic infectious arthritis. Gram stain; × 1,200.

Fig. 2.—Dextrose-brain broth culture of short-chained (indifferent) streptococci from synovial membrane in chronic infectious arthritis. Gram stain; × 1,200.

Primary cultures usually did not grow on blood agar. Repeated subcultures did not show marked variation in morphology. In view of their morphologic similarity to streptococci and the existence of mutation between certain diphtheroids and streptococci, it seems possible that the diphtheroids in arthritis may represent mutation forms of the original streptococci. However, we have no proof of this.

In order to test the elective localizing tendencies of some of the organisms isolated from arthritic tissues, four strains were injected into ten rabbits. Dextrose-brain broth cultures, approximately from eighteen to twenty-four hours old, were injected intravenously into the marginal ear vein in dosages varying from 4 to 11 cc., depending on the size of the rabbit and the density of the culture. This injection was repeated from two to four times. The rabbits were allowed to live for from four to eighty-three days. Aspiration of the joints was usually performed on the second day after the last injection. Necropsy was performed as soon as possible after death; the organs were examined for lesions, and cultures were taken from the heart's blood, joint fluid, liver and spleen.

Two strains of streptococci, one of the green-producing variety and one indifferent, obtained from the synovial membrane and one strain from the epiphyseal marrow were injected into eight rabbits. Nonpurulent effusions developed in one or more joints of five, and the periarticular structures became swollen. From six of the eight rabbits, streptococci, morphologically and culturally identical with those injected, were obtained from the joint fluid, either at the time of aspiration or at necropsy (fig. 3). Of the other organs that were cultured, the heart's blood was positive in only two instances, the liver in two instances and the spleen in none. At necropsy, the affected joints showed only the residuum of the effusion or periarticular swelling. In none of the rabbits was there any destruction of the cartilage or bone, and none of the other organs showed gross lesions (fig. 4).

Histologic study of the affected joints revealed mainly edema of the synovial membrane and periarticular capsule with infiltration of round cells which were predominantly lymphocytes and large endothelial leukocytes (macrophage cells). These were scattered diffusely throughout the entire thickness of the synovia, with here and there a more dense collection of cells. There was a tendency for some of the cells to be closely aggregated about the smaller arterioles, but this relationship of the cells to the vascular channels was not at all constant nor was it a prominent feature. In animals in which the arthritis had existed for several weeks there was evidence also of proliferation of fibroblasts (figs. 5 and 6). Sections of the synovia stained by the Gram method revealed a few scattered gram-positive to gram-negative diplococci and coccus forms of varying sizes and shapes (fig. 7). In some instances the coccus forms appeared to be dividing into small

Fig. 3.—Dextrose-brain broth culture of short-chained (indifferent) streptococci from fluid of joint of rabbit into which injections of streptococci isolated from synovial membrane from cases of arthritis were made. Gram stain; × 1,200.

Fig. 4.—Shoulder joint of rabbit into which was injected streptococci isolated from epiphyseal marrow in a case of chronic infectious arthritis; marked edema of the synovia and of the periarticular capsule without destruction of cartilage.

Fig. 5.—Synovial membrane of knee joint, showing edema and diffuse cellular infiltration; the rabbit lived thirty-seven days; × 75.

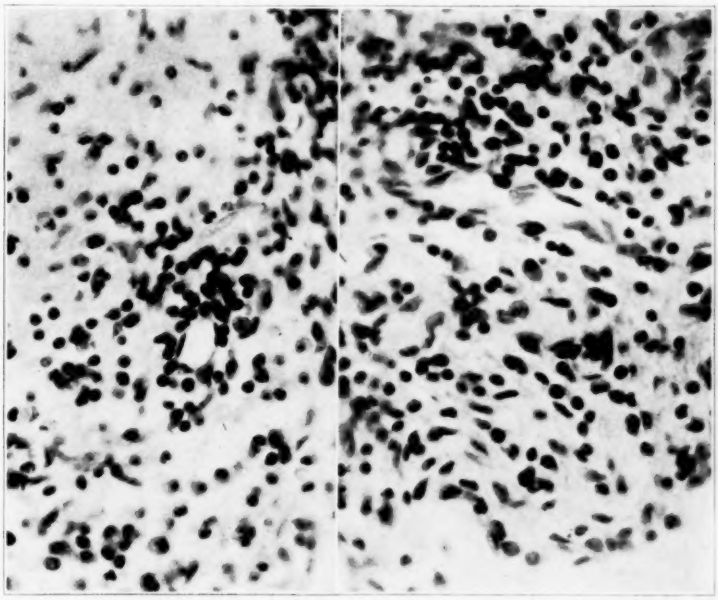

Fig. 6.—Section of synovia, showing infiltration with lymphocytes and endothelial leukocytes and beginning proliferation of fibroblasts; × 325.

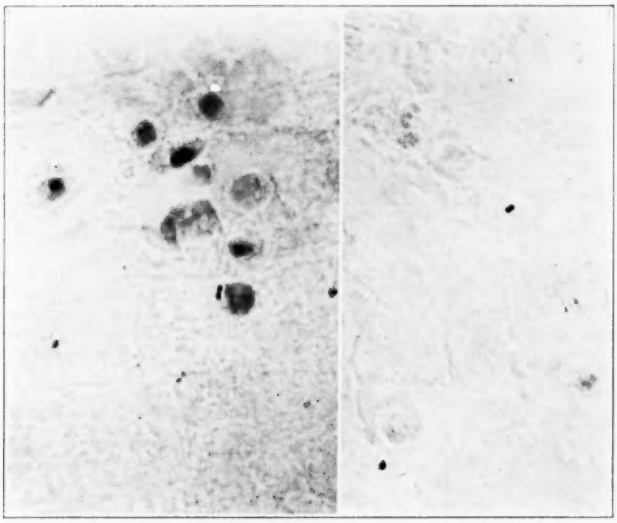

Fig. 7.—Section of synovial membrane, showing diplococci within an area of cellular infiltration. Gram stain; × 1,000.

Fig. 8.—Section of femur, showing normal cartilage of knee joint and vascular congestion in the epiphyseal marrow; × 50.

diplococci. These were found chiefly in the more superficial layers of the synovial membrane and within areas of cellular infiltration. Undoubtedly, diplococcus forms were seen in what appeared to be endothelial leukocytes. The cartilage was always intact and did not show degenerative changes. The marrow frequently showed marked vascular congestion (fig. 8), and occasionally it showed hyperplasia of its cellular elements. This was usually equally marked in the epiphyseal and diaphyseal marrow, although occasionally the marrow subjacent to the cartilage of the joint showed the more pronounced degree of hyperplasia. One of the diphtheroids obtained from the epiphyseal marrow in a case of arthritis was injected into two rabbits. In neither of these did arthritis or lesions in other organs develop. Neither could we recover the organism on culture.

COMMENT

In general, our results are in agreement with those previously reported by others, since we were able to culture bacteria from a limited percentage of arthritic tissues. It is evident also that the organism can be isolated more often from the bone-marrow of the epiphyses adjacent to affected joints than from the synovial membrane. On the contrary, our attempts to isolate bacteria from the synovial fluid were entirely unsuccessful; this is in consonance with the observations of Swett, Kinsella, and Cecil, Nicholls and Stainsby, but differs from those of Forkner, Shands and Poston. Moreover, the organisms obtained were either streptococci or diphtheroids. Within the streptococcus group, which had a distinct tendency to localize in the joints of rabbits, slight cultural variations occurred. These differences were recognizable only by the variable degree of production of pigment on blood agar, but this is not indicative of any great degree of heterogenicity. Swift, Derick and Hitchcock [22] occasionally isolated two distinct strains of streptococci from the same patient suffering from rheumatic fever at different times, and in one instance two types from one group of subcutaneous rheumatic nodules removed at biopsy.

Several significant questions occur for consideration: Is there any etiologic relationship of the bacteria isolated from arthritic tissues to the disease process? What is the explanation for the relative infrequency with which organisms can be isolated from arthritic tissues? Is this compatible with an infectious etiology of chronic arthritis? How can we reconcile the wide divergence in the percentage of positive cultures and the multiplicity of bacterial strains reported by different observers? What particular significance may be attached to the presence

22. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: Bacterial Allergy (Hyperergy) to Nonhemolytic Streptococci in Its Relation to Rheumatic Fever, J. A. M. A. **90**:906 (March 24) 1928.

of the bacteria in the epiphyseal marrow and synovial membrane and their absence from the synovial fluid?

Proof of the etiologic significance of bacteria isolated from arthritic tissues has not always been available, owing to the extreme difficulty of reproducing chronic progressive arthritis in experimental animals. This fact suggests that in man some other factors, as yet unknown, play a large part in predisposing to infection, or in initiating a process in which infection eventually assumes a dominant part. This is exemplified by one of our cases of static arthritis of the foot in which there developed subsequently the typical pathologic picture of infectious arthritis and from which we isolated a green-producing streptococcus. The nearest approach, then, to the identification of the causative organisms is by a study of their elective localizing tendencies when injected into experimental animals. In this manner we were able to show that all of these strains of streptococci gave evidence of localization in one or more joints of most of the rabbits into which injections were made. We cannot be certain of the significance of the diphtheroids that we isolated from arthritic tissues. One of these organisms did not show any tendency to localize in the joints of the rabbits. We are aware also of the caution which must be exercised in attributing pathogenic significance to them. Nevertheless, they cannot be entirely disregarded. From our knowledge of the "pleomorphism" and of the tendencies to dissociation among the streptococci and diphtheroids, it seems possible that these diphtheroids represent mutation forms of the original streptococci.

On analysis of our data, it does not seem surprising that positive cultures are obtained with such relative infrequency. As we have indicated, the average duration of the symptoms in the cases of arthritis was a matter of many years. The operations were usually performed to correct the result of ankylosis. In all cases, absolute quiescence of the process was assumed before they were deemed suitable for such operations. Even those patients who presented hydrops of the joints had usually had the effusion for a period of months before coming to operation. It would seem, then, that the organisms we obtained were only those which retained their viability despite the natural reparative processes which had been exerted by the affected tissues over periods of months or years.

It is clear that the absence of bacteria in cultures of arthritic tissues, at the time when such material becomes available to us for study, cannot be construed as proof of the noninfectious nature of the disease. On the other hand, the finding of positive cultures, even in a small percentage of cases, is strongly suggestive of its infectious etiology. It is unfortunate that circumstances do not permit of bacteriologic cultures of arthritic tissues, particularly of the epiphyseal marrow, during the early, active stages of the disease.

Of the bacteria that have been isolated from tissues in chronic arthritis, the nonhemolytic (green-producing and indifferent) streptococci have been shown to play the most prominent part. The report of Rosenow,[13] and the reports of Billings, Coleman and Hibbs, Forkner, Shands and Poston, Cecil, Nicholls and Stansby, and Richards show that these streptococci are found either exclusively or, at least, most frequently. Our own observations are in agreement with this for, excluding the occasional *Staphylococcus albus* that was found in control cultures as well as in the arthritic tissues and, therefore, may be assumed to be either a secondary invader or a contamination, the arthritic tissues yielded only nonhemolytic streptococci and diphtheroids. Yet one cannot dismiss the observations of Schüller and Crowe who have consistently found other organisms in arthritic tissues. In the absence of final proof of the etiologic relationship of any of the organisms that have been reported, we must conclude tentatively that various types of bacteria may be causative in chronic arthritis. That the apparent similarity of pathologic pictures must not imply bacteriologic unity of the etiologic agent is based on fact. Specific arthritis, which is frequently associated with bacillary dysentery and infection by *Brucella abortus,* is similar in its clinical manifestations, but it has widely different causative organisms. The predominance of the streptococci among our positive cultures, and among those reported by others, indicates that these organisms probably are of first importance from an etiologic standpoint in chronic infectious arthritis.

The relative frequency with which bacteria can be cultured from the epiphyseal bone and marrow subjacent to arthritic joints seems to us of considerable significance. Whether the infection in the subchondral marrow is the primary one and what its relation is to the general pathologic process in the joint are not clear. The pathologic studies of Milne [23] support the hypothesis of primary epiphysitis in the pathogenesis of many cases of chronic arthritis. Recent studies by Rynearson [24] on the fate of dyes injected into the cavity of the joint suggest one possible means of epiphyseal infection in arthritis. He has shown that absorption of dyes from the synovial sac occurs readily and that large macrophages laden with phagocytosed foreign material eventually reach the reticulo-endothelial system, of which the marrow is the most extensive part. It is conceivable, therefore, that many of the bacteria that attack primarily the various structures in and about the joint eventually find their way to the reticulo-endothelial system where secondary foci may be established. Similarly, we may explain the absence of bacteria in the fluid of the joint in long-standing cases

23. Milne, L. S.: Chronic Arthritis, J. Path. & Bact. **16**:199, 1911.

24. Rynearson, E. H.: Studies on the Physiology of Joints: Mechanism of Absorption of Various Substances from Synovial Cavity, Proc. Staff Meet., Mayo Clin. **3**:171, 1928.

of arthritis by the phagocytic action of the cellular elements in the fluid. The potency of such phagocytosed bacteria to establish secondary infectious foci in the marrow is, however, unknown. Neither do we have conclusive data as to the part played by primary epiphyseal foci of infection in the pathogenesis of chronic arthritis. It is certain, however, that too little attention has been given in the past to bacteriologic studies of the epiphyseal marrow subjacent to arthritic joints. There is, it is true, a paucity of such material which is available for study. Nevertheless, it would seem that relentless study of this problem may yield data of considerable importance to our understanding of chronic arthritis.

SUMMARY AND CONCLUSIONS

1. Nonhemolytic streptococci were isolated from the epiphyseal marrow and bone, from the synovial membrane and from the cartilage obtained from joints affected with chronic nonspecific arthritis.

2. The synovial fluid from these cases did not yield organisms other than those from occasional contamination.

3. The epiphyseal marrow and bone yielded bacteria more frequently than any of the other tissues. This may indicate a significant site of infection in the pathogenesis of arthritis which has not been given sufficient consideration in the past.

4. Cultures of control tissues from joints other than those of nonspecific arthritis yielded organisms other than streptococci. These could be ascribed either to secondary infection or to accidental contamination.

5. Several of the streptococci isolated from arthritic tissues showed marked elective affinity for joints when injected intravenously into rabbits. One diphtheroid which was similarly injected did not localize in the joint.

6. The relative infrequency with which organisms were grown from arthritic tissues is probably due to the long duration or inactivity of the disease when the material became available for study.

7. The negative cultures from tissues of the joints are not proof of the noninfectious nature of the disease; the presence of bacteria, even in a small percentage of cases, is strongly suggestive of infection in the etiology of chronic arthritis.

8. The nonhemolytic green-producing and indifferent streptococci seem to be of first etiologic significance in chronic arthritis, in confirmation of the previous work of Rosenow [25] and others.[26]

25. Rosenow, E. C.: The Etiology of Articular and Muscular Rheumatism, J. A. M. A. **60**:1223 (April 19) 1913; Studies in Elective Localization: Focal Infection with Special Reference to Oral Sepsis, J. Dent. Research **1**:205, 1919.

26. Meisser and Brock (footnote 2, first reference). Nakamura (footnote 2, second reference). Nickel (footnote 2, third reference). Poynton and Paine (footnote 10). Billings (footnote 12). Forkner, Shands and Poston (footnote 16). Cecil, Nicholls and Stainsby (footnote 17). Richards (footnote 19).

LIPOID NEPHROSIS

PATHOLOGY, GENESIS AND RELATION TO AMYLOIDOSIS *

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CHICAGO

As numerous as are the articles and discussions on lipoid nephrosis, so rare are the actual cases anatomically proved and reported. Few subjects in medicine have enjoyed as much speculation on as little material support or suffered as much the consequence of confusion. Of the small number of cases clinically considered, few are checked by autopsy for the excellent reason that usually the patients do not die. The great majority of those which are so checked, prove, contrary to the best supported clinical diagnoses, to be only glomerulonephritis with a nephrotic component (einschlag). Many others are so tangled up with amyloidosis that they are ordinarily ruled out of argument. The specific renal tubule damage in pregnancy and in various infections and intoxications account for still other pretenders.

Aschoff finally denied altogether the existence of a genuine lipoid nephrosis. Wells [1] stated that he had looked all his life for a pure case in an adult. He had many clinically classic cases of nephrosis in which at autopsy the gross anatomic picture was just as classic of nephrosis, but microscopically he always found, to his disappointment, a subacute or chronic glomerulonephritis. Loehlein [2] and Elwyn [3] insisted that all the cases of so-called primary lipoid nephrosis are in reality primarily glomerulonephritides, no matter how the inflammatory is later obscured by the nephrotic element. Even those who do admit the reality of lipoid nephrosis, hesitate, as does Herxheimer, at the possibility of nephrotic contracted kidneys. Klemperer [4] affirmed that he had never believed in lipoid nephrosis until he had seen for himself a true case. Subsequently, he even found one with nephrotic contraction. Nephrosis may be counterfeited so closely by other conditions that no cautious pathol-

* Submitted for publication, Nov. 23, 1929.

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1. Wells, H. G.: Discussion of Bell, L.: Lipoidnephrosis, read at meeting of Am. A. Pathologists & Bacteriologists, Chicago, 1929, Am. J. Path. **6**:541 (July) 1929.

2. Loehlein, M.: Ueber Fettinfiltration und fettige Degeneration der Niere des Menschen, Virchows Arch. f. path. Anat. **180**:1, 1905.

3. Elwyn, H.: Nephritis, New York, The Macmillan Company, 1926; The Pathogenesis of Lipoid Nephrosis, Arch. Int. Med. **38**:346 (Sept.) 1928.

4. Klemperer, Paul, in discussion of Kohn, J.: Lipoid Nephrosis, Tr. New York Path. Soc. Arch. Path. **6**:528 (Sept.) 1928.

ogist, unless it has been his rare good fortune to see one of the few anatomically established cases, will accept it as an entity.

Yet from time to time cases are reported which even the firmest skeptic cannot deny. Among these may be mentioned those of Munk,[5] Volhard,[6] Fahr,[7] Loewenthal,[8] Kaufmann,[9] Kohn,[10] Murphy,[11] Cabot [12] and Rachmilewitz.[13] Cases of nephrotic contracted kidneys are even more rare. Yet irrefutable ones have been described by Volhard, Munk, Kaufmann, Bohnenkamp and Bergstrand. Almost all of them occurred in syphilitic patients. That lipoid nephrosis, though rare, may indeed occur without any demonstrable nephritis and distinct from amyloidosis and that independently it may be a cause of death was demonstrated by an unusual series of autopsy material which I had the opportunity to study.

This material also served to recall attention to the many pitfalls of the clinical diagnosis. It is known, in particular, that cases of chronic nephritis with a nephrotic component can reproduce accurately every chemical and clinical detail of a pure nephrosis. Amyloidosis may be buried out of view under the syndrome of lipoid nephrosis or, on the other hand, may completely overshadow it. The clinician is obliged to venture his rare diagnosis of nephrosis with great caution and reserve. Accordingly, the opportunity was also taken to try out a clinical test which though not widely known in this country has been used considerably abroad to help somewhat to alleviate these diagnostic difficulties.

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5. Munk, F.: Pathologie und Klinik der Nierenerkrankungen, Berlin, Urban & Schwarzenberg, 1925; Zur Pathogenese der nephrotischen Schrumpfniere, Virchows Arch. f. path. Anat. **226**:81, 1919.

6. Volhard, F., and Fahr, T.: Die Brightische Nierenkrankheit, Berlin, Julius Springer, 1914.

7. Fahr, Thomas: Pathologische Anatomie des Morbus brightii, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, vol. 6, p. 172.

8. Loewenthal, Karl: Weitere Beitrage zur Frage der Lipoidnephrose, Virchows Arch. f. path. Anat. **261**:109, 1926; Weitere Beitraege zur Frage der Lipoidnephrose, Beitr. z. path. Anat. u. z. allg. Path. **79**:497, 1928.

9. Kaufmann, J., and Mason, E.: Nephrosis, Arch. Int. Med. **35**:561 (May) 1925.

10. Kohn, J.: Lipoid Nephrosis, Arch. Path. **6**:528 (Sept.) 1928.

11. Murphy, F. D., and Warfield, L. M.: Lipoid Nephrosis, Arch. Int. Med. **38**:449 (Oct.) 1926.

12. Cabot, R.: Fatal Albuminuria without Nephritis, New England J. Med. **199**:97, 1928.

13. Rachmilewitz, M.: Hypercholesterolemia Associated with Hepatosplenomegaly and Nephrosis, J. A. M. A. **93**:604 (Aug. 24) 1929.

PURE LIPOID NEPHROSIS

CASE 1.—*History.*—A colored boy, 3 years old, was brought to the Cook County Hospital in August, 1928, suffering from a severe generalized edema. He was discharged in January, 1929, as improved. The boy was tolerably well until April, 1929, when puffiness about the eyes began, and he was readmitted to the hospital.

He had been born after a normal delivery at full term. He was breast fed; cod liver oil and orange juice had been given. His development was normal. Chickenpox had been his only ailment before the edema began. The mother was 29 years old, living and well; she had borne 3 children, with no miscarriages.

Physical Examination.—The results of physical examination were negative, except for the puffiness about the eyes. No other complaints or observations were registered. The facial edema gradually increased and spread until, within two weeks after entrance, it was severe and involved the entire body. The pharynx showed a slight injection, and the temperature varied from normal to 101 F.

Laboratory Observations.—Doubly refractile lipoid droplets were found in the urine. The albuminuria was severe, with many finely granular casts but no red blood cells. The erythrocyte count was normal, 5,200,000; the leukocyte count, 9,650 per cubic millimeter.

The report on the blood chemistry was as follows: Urea nitrogen amounted to 13.6 mg. per hundred cubic centimeters. The cholesterol was elevated to 416 mg. There was a reversed albumin-globulin ratio. Serum albumin was decreased to 1.64 per cent as compared with a normal range of from 4.6 to 6.7 per cent.[14] The serum globulin was at the high level of 2.3 per cent as compared with the normal variation of from 1.2 to 2.3 per cent.

Clinical Diagnosis.—The diagnosis was nephrosis and pharyngitis.

Treatment and Course.—The child was placed on a diet high in protein, and for three days given ammonium chloride, 5 grains (0.3 Gm.) three times a day. On April 27, he was given 0.25 cc. of sodium mercurisalicylallylamido acetate (solyrgon) intravenously. The edema continued to increase, and three days later, on April 30, a second dose was given. He died unexpectedly several hours after the second injection.

Postmortem Examination.—The marked puffiness of the face, especially of the eyelids, the moderate pitting edema over the entire trunk and the severe edema of the genitalia were striking observations. The lips were pale. The abdomen was distended; its cavity contained 400 cc. of a chyliform fluid. Each pleural cavity contained 100 cc. of similar fluid.

The heart was of normal weight, 68 Gm. The wall of the left ventricle was 10 mm. thick; that of the right, 2 mm. thick. The myocardium was pale and soft. The lungs were moist with foamy fluid. The liver was enlarged to 690 Gm., and was pale and moist. The spleen weighed 68 Gm. and was firm; its corpuscles were enlarged. The lymph nodes of the abdominal cavity were enlarged and waterlogged.

The kidneys were enlarged, and together weighed 200 Gm. as compared with the normal, at that age, of 100 Gm. The capsule stripped easily, leaving a smooth, pale gray surface. On surfaces made by section, the cortex was 8 mm.

14. Myers, V. C.: Chemical Changes in the Blood and Their Clinical Significance, Physiol. Rev. **4**:279, 1924.

wide, pale gray with opaque, yellowish-white patches and lines, radiating toward the pelvis. The medulla was deeper gray and sharply differentiated from the cortex.

Microscopic Examination.—The glomeruli of the kidney were normal in size, number and distribution, with unchanged cellularity and tufts moderately filled with blood. Many of the Bowman spaces were narrow and empty. Others were wide and filled with a homogeneous pink material containing a few fine lipoid

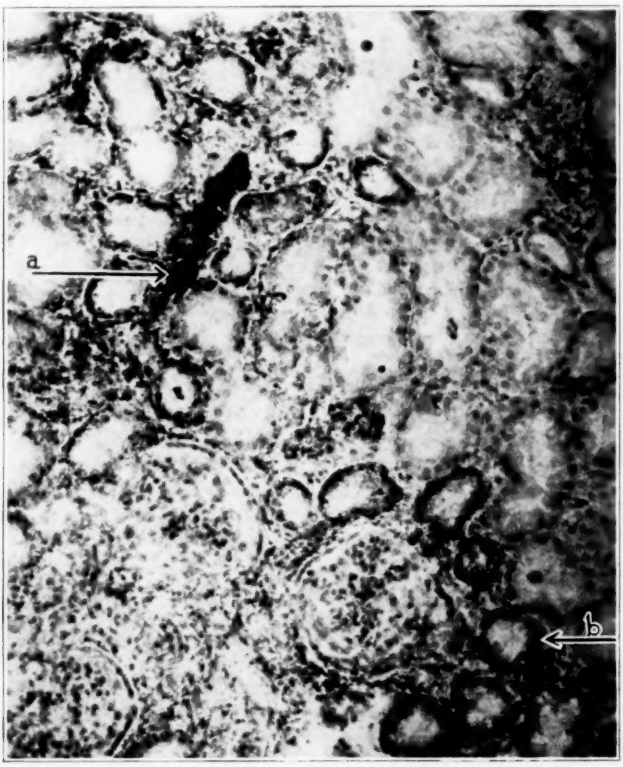

Fig. 1.—Kidney showing extensive lipoid infiltration in single proliferated sessile histiocytes of the interstitial tissue and in groups of them (*a*), and in the convoluted tubuli of the first order (*b*). The capsular epithelium of the glomeruli is somewhat swollen, but the glomeruli are intact. Sudan III; hematoxylin; × 150.

granules. The parietal lining of the capsules was moderately swollen and bulged into the spaces. Fine fat droplets were scattered through its cells, as well as through those of the visceral glomerular epithelium.

Groups of convoluted tubuli arranged closely about the glomeruli showed a large amount of fat in their lining epithelium. This fat, which was doubly

refracting, had accumulated mostly near the base of the cells. The cells were enlarged, so that the lumen of these convoluted tubuli of the first order was narrow. Their cytoplasm was oxyphilic and granular, but had no hyaline droplets. The nuclei were well preserved, enlarged, with well defined chromatin structure. An occasional fat-filled cell and homogeneous pink cast was found free in the lumen of these tubules.

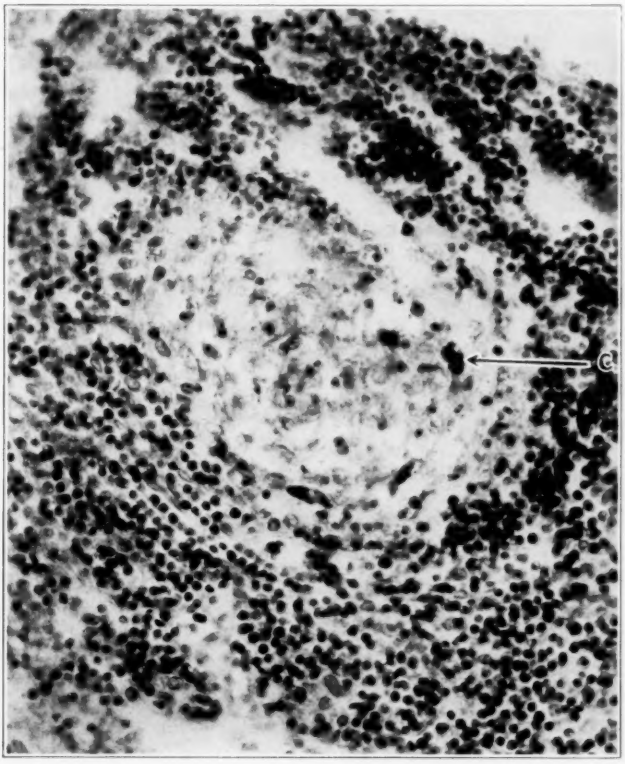

Fig. 2.—Lymph node; germinal follicle with swollen and proliferated reticulum cells containing fine lipoid granules. Sudan III; hematoxylin; × 300.

The other convoluted tubules and the ascending limbs of Henle's loops showed but slight fat, and no epithelial enlargement. The collecting tubules and the descending limbs of Henle's loops were unchanged, except for the granular and homogeneous casts in their lumen.

The interstitial tissue was somewhat edematous, separating the tubules by small, loose spaces. Especially in the deeper layers of the cortex, it contained many large, oval or branched cells with an ample cytoplasm and deeply stained nuclei. These cells were loaded with fat which gave a brilliant double refrac-

tion. The vessels were unchanged, except for a small amount of fat scattered in the intima and adventitia of the smaller arteries.

In the liver, the Kupffer cells were stuffed with lipoid granules which filled their branches. There was a little fat in the liver cells. It was not doubly refractile.

The follicles of the spleen contained distinct, lightly stained centers. They were composed of elliptical and fusiform cells with pale-stained, oval nuclei. The cytoplasm of these cells contained fine and medium-sized lipoid granules, which were doubly refracting. Between these cells there were a few lymphoblasts which did not contain fat. The endothelium of the sinuses appeared slightly swollen, and in places contained fine, dustlike lipoid granules.

In the mesenteric lymph nodes, the centers of the cortical follicles were composed of elongated, swollen or branched cells which were filled with lipoid droplets. The sinuses were wide; their lining was swollen and showed a fine lipoid infiltration.

In the alveolar spaces of the lung were narrow, elongated cells, adjacent to the capillaries. They contained small fat droplets. Single large round cells with fat droplets were seen free in the alveolar spaces.

All layers of the cortex of the suprarenal glands were rich in lipoid material. There were single small fat droplets in the cells of the medulla.

The reticulum cells of the thymus were filled with lipoid droplets. The plasma in the vessels even stained a light orange yellow with sudan III.

Anatomic Diagnosis: The anatomic diagnosis was: lipoid nephrosis; generalized anasarca; chylous ascites and bilateral hydrothorax; diffuse edema of the lungs; edema of the liver; hyperplasia of the lymph nodes, and of the lymph follicles of the spleen, and parenchymatous degeneration of the myocardium.

Comment.—Pure lipoid nephrosis does exist. The case just described cannot summarily be dismissed as a form of nephritis. As long as one can muster any appreciable inflammatory changes, it may be conceded Elwyn and his school that the nephrosis is only a secondary component to a slight but healed nephritis. But when, in cases such as this, the most exhaustive search fails to reveal the slightest evidence of renal inflammation, one is left without anatomic support for such a theory.

In nephritis, with a well established glomerular damage, some tubular injury is expected. But when the tubular and interstitial changes appear in a severity out of all proportion to the insignificant or totally absent glomerular ones, the histologic picture loses all resemblance to nephritis, and from it these cases must be sharply separated. Even if some glomerular changes are noted, such as the swelling of the parietal epithelium of Bowman's capsule and the lipoid infiltration of the glomerular tufts, they bespeak a degenerative rather than an inflammatory process. They can be ranked only as the glomerulonephrosis which accompanies the overwhelming tubulonephrosis. Even if an occasional glomerulus should be found with a definite inflammatory reaction, with increased cellularity, infiltrations and decreased blood content of the tufts, one would still have no right to charge the whole histologic

picture to a nephritis. For this trifling inflammatory change might just as well be only an incidental complication, secondarily engrafted on a well defined, chronic lipoid nephrosis. Furthermore, this slight glomerulitis could never account for the widespread tubular and interstitial damage. It is this disparity which forces one to recognize in such cases the independence from nephritis of a pure lipoid nephrosis.

Nephrosis is grouped with the renal diseases, yet the kidneys are only byways in its pathogenesis. Fundamental in its genesis is some disturbance in lipoid-protein metabolism. The cause of this disturbance is, to present knowledge, uncertain. In children, an infectious process in the upper part of the respiratory tract, such as occurred in my case, is generally inculpated. A history of numerous infections is often obtained in cases of nephrosis, but no more frequently than in cases of other diseases. It is to be expected that infections will crop up incidentally in the history of any chronic ailment. Munk stressed the importance of syphilis. Cases appear frequently with tuberculosis, but are often then mixed with amyloidosis. Various endogenous and exogenous intoxications, anaphylaxis, endocrine disturbance, constitutional predisposition have all been invoked, but none proved. It has been set up as one of the diseases of the reticulo-endothelial system, but its histologic aspects and clinical picture bear only vague resemblance to them. It differs as widely also from the pictures of lipemia in cholemia and diabetes.

Be its cause what it may, nephrosis is a special type of disturbance of lipoid-protein metabolism, just as diabetes mellitus is a specific disturbance of carbohydrate metabolism. This analogy led Epstein [15] to suggest as a substitute for "nephrosis," the term "diabetes lipoid-proteinicus." "Lipoid-protein diabetes" is a better term than "nephrosis," for it directs attention more properly to the generalized disturbance. The kidneys assume prominence only because they are heavily involved in their rôle as excretory organs for the products of disturbed metabolism. Secondarily, they are damaged, but nephrosis is primarily not a disease of the kidney.

Indeed, the rôle of the liver is coming to be regarded as of greater consequence than that of the kidney. That a definite damage of the liver exists is indicated by Knauer's [16] observation in nephrotic children of a symptomless but definite hypoglycemia. The loss of trypanocidal activity by the blood serum in nephrosis, as well as the general water imbalance, also confirms the assumption of a liver deficiency, for the

15. Epstein, A.: Ueber Diabetes albuminuricus, die sogenannte chronische Nephrose, Arch. Verdauungskr. **44**:31, 1928.

16. Knauer, Hans: Neue Berunde bei der Lipoidnephrose, Klin. Wchnschr. **7**:987, 1928; Ist die Nephrose eine Nierenerkrankung? Med. Klin. **23**:862, 1927.

liver is normally active in these functions. As anatomic evidence, one can cite only the extensive fatty changes found.

Whatever is its cause or its line of attack, the generalized cellular damage with its disturbance of lipoid-protein metabolism leads to a profound alteration in the chemistry of the body tissues and fluids. There is a massive albuminuria with a marked decrease in the albumin content of the blood serum. The albumin in the urine is not simply that which has been lost from the blood.

The loss is far too large to be so accounted for. Nor does it come from the food, for feeding huge quantities of protein does not aggravate it. The albuminuria is endogenous, not exogenous. It is derived from the breaking down of cells, from the altered protein metabolism all over the body and especially, according to Andrews,[17] from the liver.

This albumin would pile up in the blood were it not so readily able to pass through the kidneys. Munk considered the kidneys to be permeable to it because it is an abnormal, an altered albumin. By passing an electric current through serum, he found a shift of its proteins toward a euglobulinemia. When he then perfused it through a dog's kidney, he obtained an albuminuria, and a marked reduction in the albumin content of the serum. The globulin content remains normal because this protein has larger molecules which cannot pass through. It may even rise as a result of the cellular disintegration and the shift of proteins described by Munk. The globulin content may thus come to exceed the much diminished albumin, and there is a reversal of the normal albumin-globulin ratio.

In like manner, the generalized disturbance in cellular lipoid metabolism unloads a large quantity of fats, particularly cholesterol into the serum. This cholesterolemia, too, is not exogenous but endogenous. For huge quantities of cholesterol may be fed without yielding the slightest rise in the cholesterolemia. The excessive cholesterol in the blood comes from the damaged cells all over the body. Buerger[18] regarded it as a different kind of cholesterol from that which is seen in the lipemias of early starvation or pregnancy or narcosis or diabetes or cholemia. He distinguished that of nephrosis as an abnormal, a cytolytic cholesterolemia.

Normally, any excess of cholesterol is excreted partly by the skin, but mostly by the liver through the gallbladder and intestinal tract. For a time, the liver may be adequate in its discharge of the excessive cholesterol, but if it is damaged or if it is exhausted by this undue strain,

17. Andrews, E., and Thomas, W. A.: Origin of Urinary Proteins, J. A. M. A. **90**:539 (Feb. 18) 1928.

18. Buerger, Max: Der Cholesterinhaushalt beim Menschen, Ergebn. d. inn. Med. u. Kinderh. **34**:661, 1928.

lipoid piles up in the blood, and the serum becomes milky with it. The serum of a diabetic or cholemic patient may be rich in fat, yet none appears in the urine. A lipoidemia appears in early starvation, yet normally only slight traces of cholesterol pass through the kidney (Gardner [19]). The abnormal, cytolytic cholesterol of nephrosis, as compared with the retention cholesterol of cholemia, the transport cholesterol of starvation, etc., can, however, more readily pass through the kidneys and does so in huge quantities. In analogy, I mention that the bilirubin of obstructive jaundice is chemically the same as the bilirubin of hemolytic jaundice, yet the former can pass through the kidneys while the latter cannot. A massive lipoiduria follows, and doubly refractile cholesterol crystals are found in the urine.

On the kidneys, then, is thrown the chief load of evacuating the abnormal lipoids and protein. Because of its status as the pathway of excretion, a series of renal changes is secondarily induced. Four stages are herein distinguished: (1) infiltration, (2) degeneration, (3) interstitial tissue changes and (4) contraction.

At first there is only a hyperactivity of the renal epithelium cells. Their nuclei are large, with well preserved chromatin structure. Their cytoplasm is enlarged, filled with granules and droplets, stuffed with isotropic and anisotropic lipoids. They are "congested with the traffic of excretion." This affects, chiefly, the proximal convoluted tubuli of the first order, those closely grouped about the glomeruli. But it also appears in the parietal layer of the glomerular epithelium, within the glomerular tufts, and in traces through the whole remaining length of the renal units up to the collecting tubules.

This diffuse glomerulonephrosis and tubulonephrosis with heaviest involvement of the first tubular convolutions is in early stages only infiltrative. There is no evidence of degeneration. Later, as the cells become exhausted by this functional strain, they atrophy. A secondary tubular damage ensues. The nuclei become pyknotic, the cytoplasm hyalinized. Desquamated cells are seen in the lumen of the tubules, and atrophied cells in their walls. If the damage is not too great, active regeneration is seen in the tubular epithelium. Thus ends the second stage.

The glomeruli are all this time microscopically unchanged. The cholesterol in the urine is not simply that which comes from the renal tubular degeneration. The substance of all the renal tubules together could produce only a small part of the cholesterol found in the urine. Tubular degeneration just as far advanced is seen in other conditions, such as the acute infections or diabetes, without a trace of lipoid appear-

19. Gardner, J., and Gainsborough, H.: Determination of Cholesterol and Cholesterol Esters in Urine, Biochem. J. **19**:667, 1925.

ing in the urine. The cholesterol in the urine can therefore be only partly that which is in the degenerated tubular epithelium; it comes mostly from the blood. The cholesterolemia, in turn, is derived from the disturbed metabolism all over the body.

Not every lipoid infiltration or degeneration of the kidney is lipoid nephrosis. These changes are seen as well after experimental adrenalectomy (MacMahon,[20] Gunn [21]), in the lipemia of diabetes, in acute infections, in cholemia and in chronic nephritis without a nephrotic component. The tubular cells may be filled with lipoid. Singly and doubly refractile fat may be abundant in the glomerular parietal epithelium and in the tufts. Fat may even render the blood serum and the contents of the Bowman's spaces light orange in the sudan III stain. But fat changes are not "nephrosis," until the third series of changes is demonstrated.

The most characteristic change in the kidney in nephrosis is the reaction of the interstitial tissue. The sessile histiocytes of the stroma proliferate. They draw in their branches, swell up and become packed with singly and doubly refractile lipoids. This was the most prominent feature in the sections stained with sudan III of my first case. Rachmilewitz [13] and Murphy [11] found the same changes. Stoerk believed that they arise through the absorption by the reticulum and endothelial cells, of the remains of the few tubular epithelium cells which from time to time disintegrate. The fat-laden, proliferated groups of histiocytes are the refuse heaps of the slow and remittent epithelial cell exhaustion. This is the most definite, positive histologic criterion of nephrosis.

All over the body, the cells of the reticulo-endothelial system participate in the burden of lipoid disposal. In the lymph nodes, the reticulum cells of the follicles are packed with singly and doubly refractile lipoids. The Kupffer cells of the liver, the interstitial cells of the lung parenchyma, the reticulum cells of the spleen are similarly affected. The interstitial cells of the kidneys share in this process. Just such changes are seen also in any of the diseases of the reticulo-endothelial system, such as Niemann-Pick's disease. But in these alone, the interstitial renal changes are slight. It is when to them are added the interstitial cell proliferation and infiltration of lipoid from the exhausted tubular cells that there is truly a nephrosis.

In only one condition other than true lipoid nephrosis can such marked renal interstitial fatty changes be found. This is chronic nephritis with a nephrotic component. But here the presence of inflammatory

20. MacMahon, H. E., and Zwemer, R. L.: Pathologic Histology of Adrenalectomized Cats, Am. J. Path. **5**:491 (Sept.) 1929.

21. Gunn, F. D.; Cori, C. F., and Hartman, F. A.: Lipoid Nephrosis in Adrenalectomized Rats and Guinea-Pigs, Proc. Soc. Exper. Biol. **25**:410, 1928.

glomerular changes and the absence of the gross disproportion between the glomerular and tubular damage would establish its differentiation from lipoid nephrosis.

With all these changes described, even to the end of the third stage, renal function is still well maintained (Holmes [22]). There is no hematuria, no anemia, no retinitis, no high blood pressure, no cardiac hypertrophy. The phenolsulphonphthalein test is normal, and there is no azotemia even on a diet high in protein. Only in the stage of active edema is there retention of water and salt. The Aldrich test injection is then rapidly absorbed.[23] The Mosenthal test shows good power of urine concentration, but a delayed excretion of ingested fluids. Diuretics fail to act until the edema of itself begins to subside.

For the edema is extrarenal (Fanconi [24]). It is not a result of inability of the kidneys to excrete water (Koranyi [25]). If it were, there would be a hydremia in nephrosis. Actually, the blood is thicker than normal in nephrosis, so that hemoglobin and red blood cell counts may be excessive. The edema is a result of water retention by the tissues. The kidneys would well be able to excrete this water, if the fluid-soaked tissues would only release it.

The desperate clinical attempts to relieve the edema meet, therefore, with variable success. Among those tried may be mentioned a diet high in protein and low in fat, restriction of water and salt, thyroid therapy (Epstein [26]), antisyphilitic treatment in syphilitic cases, and the use of calcium, parathyroid (Lewis [27]), diuretin, theophylline, digitalis, ammonium chloride or nitrate and sodium mercurisalicylallylamido acetate. The number of the methods suggested is evidence enough of the lack of reliability of any one. In the case described, death occurred soon after the second injection of sodium mercurisalicylallylamido acetate. But Bernheim in 1,000 injections did not observe the slightest toxic symptoms from it. Herzky, Brunn, Agnew and Barker and O'Hare [28] have all had the same innocuous results. In view of this, the sodium mercurisalicylallylamido acetate can in no way be held

22. Holmes, W. H.: Lipoid Nephrosis, Illinois M. J. **54**:300, 1928.

23. Aldrich, C. A.: A Study of the Clinical Course of Generalized Edema, J. A. M. A. **84**:481 (Feb. 14) 1925.

24. Fanconi, G.: Zur Oedemfrage, Jahrb. f. Kinderh. **110**:12, 1925.

25. Von Koranyi, A.: Pathogenese der nephrotischen Wasser-Retention, Mitt. d. Gesselsch. f. inn. Med. u. Kinderh. in Wien. **24**:15, 1925.

26. Epstein, A.: Further Observations on the Nature and Treatment of Chronic Nephrosis, Am. J. M. Sc. **163**:167, 1922.

27. Lewis, D. S., and Seriver, W.: The Response of Chronic Nephrosis to Parathyroid Medication, Ann. Int. Med. **2**:66, 1928.

28. Barker, M. H., and O'Hare, J. P.: The Use of Salyrgan in Edema, J. A. M. A. **91**:2060 (Dec. 29) 1928.

responsible for the premature termination of this case. That it did any good is likewise unproved.

The fourth stage, the end-result of lipoid nephrosis, is demonstrated in case 2. The material of this case was placed at my disposal by Dr. Milton Bohrod of the University of Illinois Research Hospital.

LIPOID NEPHROSIS WITH NEPHROTIC CONTRACTION

CASE 2.—*History.*—A white, Irish-American painter, 26 years old, first entered the Cook County Hospital on April 14, 1928. He said that he had had a chancre in 1927, for which he took eleven injections of neoarsphenamine and thirty of mercury. During the "rest period" following this first course, and just as he was about to start a second, he began to have attacks of abdominal colicky pains and diarrhea. These cleared up, but a generalized edema set in. The swelling was noticed first and most severely in the legs, but it did not there subside on rest. It slowly spread to the abdomen and face.

Physical Examination.—He was somewhat dyspneic on exertion, but there was no orthopnea. A mild cough was associated with a pharynx that showed injection. A slight pain in the chest followed for a short time. Dullness and distant breath sounds were obtained over the right lower pulmonary lobe. But this soon subsided. The abdomen was moderately distended with fluid. The heart was not enlarged.

Laboratory Examination.—He appeared pale, but examination of the blood showed that the hemoglobin was fully 80 per cent and the erythrocyte count 4,000,000. The blood pressure was normal, 126 systolic and 84 diastolic. The Wassermann reaction was negative. The blood chemistry showed a urea nitrogen of 20 and a creatinine content of 1.7 mg. per hundred cubic centimeters. There was marked albuminuria, also a few granular casts but no red blood cells in the urine. The Mosenthal test showed good power of concentration (1.030).

Clinical Diagnosis.—The clinical diagnosis rested between lipoid nephrosis and parenchymatous nephritis (mercurial).

Further Course.—The patient was released from the hospital on May 2, 1928, apparently recovered, but he returned on June 11 with a recurrence of his first clinical picture. At this time, the blood cholesterol was found elevated to 416 mg. per hundred cubic centimeters. While the patient was in the medical ward, a swelling developed in the region of the thyroid gland. There was great pain, with local heat and induration with central fluctuation. Aspiration yielded thick pus. A suppurative thyroiditis was diagnosed. The abscess was opened and drained. It healed completely, and the patient left the hospital late in June.

In August, he suffered a second recurrence of the edema, and entered the University of Illinois Research Hospital. He was found to have a generalized anasarca, ascites and a bilateral pleural effusion. The heart was not enlarged. The blood pressure was normal, about 115 systolic and 70 diastolic.

Laboratory Examination on Third Admission.—Paracentesis yielded 5,500 cc. of a pseudochylous fluid, the specific gravity of which was 1.004. No doubly refracting lipoids were found in it. Its lipoid was all isotropic.

The renal function was now distinctly impaired. On the Mosenthal test, the night urine equaled the day urine in quantity, and its specific gravity varied only from 1.007 to 1.010. Only 2 per cent of the phenolsulphonphthalein was excreted in three hours. There was severe albuminuria with few hyaline casts, but no red blood cells.

Blood chemistry returned successive cholesterol readings of 714, 1,136, 384, 455 and 625 mg. per hundred cubic centimeters. The nonprotein nitrogens were 45, 51, 46 and 65. The creatinines were 3.76 and later 4.29. The carbon dioxide-combining power of the plasma was 23. The chlorides returned 651 and 597 mg. per hundred cubic centimeters.

Anemia had developed with 43 per cent hemoglobin, an erythrocyte count of 2,260,000 and a leukocyte count of 7,000 per cubic milligram. The basal metabolic rate was depressed to minus 26 per cent. The Wassermann reaction was negative.

Clinical Diagnosis.—The clinical diagnosis still rested between lipoid nephrosis and chronic tubular nephritis of syphilis, mercurial or arsenical origin.

Further Course.—Sodium thiosulphate was given intravenously, because of the possibility of metallic poison. Clinically, the patient recovered.

He returned, however, on several occasions with a fourth, fifth and finally a fatal sixth recurrence in November, 1928, seven months after the onset of the illness. Even at the last attack, the blood pressure was only 118 systolic and 90 diastolic, and there was no cardiac hypertrophy or retinal changes. The patient suffered, however, from intermittent diarrhea, nocturia, polyuria and nausea and vomiting, which became progressively more severe until his death.

Postmortem Examination.—There was slight edema of both feet and ankles. The abdomen was greatly distended by 8,000 cc. of opalescent, yellowish, milky fluid. The peritoneum was dull, with nodular areas of thickening. The pericardial sac contained 75 cc. of clear, straw-colored fluid.

The heart was small and contracted. It weighed only 220 Gm. The myocardium was brown and friable.

The liver weighed 1,350 Gm. It was firm and yellowish brown. Its markings were indistinct. The spleen weighed 190 Gm.; its consistence was diminished.

The kidneys were both small. The right weighed 72 Gm.; the left, 92. The capsule stripped readily, leaving a smooth, yellowish-white surface with an occasional smooth elevation. The cortex was wide and deep yellow. The medulla was more brown and sharply demarcated from it.

Microscopic Examination.—There was at once evident, a striking disproportion between the pronounced interstitial and tubular changes and the slight glomerular and vascular changes in the kidneys. The latter were grossly insufficient to account for the former, but impressed one as being rather a result of them.

The tubules were widely separated by the marked increase of interstitial tissue. In the medulla, Henle's loops and the collecting tubules were all widely dilated by homogeneous casts. In the cortex, some of the convoluted tubules were dilated; others were altogether collapsed. There was a diffuse atrophy of the renal epithelium, especially that of the convoluted tubuli, which were lined by low cuboidal cells. There was no desquamation, no hyaline droplets, no mitoses, no enlarged cells or other evidence of either active regeneration or active degeneration. Only a few, fine fat droplets were scattered through the epithelial cells of the convoluted tubuli of the first order. As compared with those in the first case described, the tubular changes had apparently become far advanced, but had quieted down.

The increase of interstitial tissue even exceeded the tubular atrophy in severity. In places, there were large areas in which the tubules had entirely disappeared, and only groups of glomeruli with dense interstitial tissue remained. This tissue was composed of lymphocytes, fibroblasts and groups of large

branched or swollen round cells. The cells of most of the latter groups were stuffed by isotropic and anisotropic fat. This interstitial tissue proliferation encroached on the glomeruli in the form of dense, concentric, pericapsular thickenings.

As compared with the usual picture of chronic nephritis or of renal arteriolosclerosis, the glomerular changes which accompanied these severe parenchymatous ones were unexpectedly slight. Most of the glomeruli had a normal or but

Fig. 3.—Kidney; intact glomerulus surrounded by far advanced atrophy of the tubules, pericapsular connective tissue thickening and marked increase in the interstitial tissue. Mallory aniline blue; × 275.

slightly decreased blood content. Their capillaries were discrete, with lumen somewhat narrowed in places, but with no synechiae. The tufts were somewhat smaller than normal. This shrinking gave an apparent slight increase in cellularity, but there was no actual proliferation or infiltration of cells in the tufts. The Bowman's spaces were dilated, and many contained a pink homogeneous content. The parietal capsular epithelium showed a slight enlargement and proliferation under the thick pericapsular ring of connective tissue.

In some of the glomeruli, an occasional capillary loop was seen with small lumen. Other loops were obliterated by fusion of their walls and almost complete melting of structure into a hyaline mass. An occasional whole glomerulus was similarly almost or completely reduced to a hyaline mass showing a few nuclei and other remnants of capillary structure. The medium-sized arteries were unusually tortuous, apparently slightly thickened, but otherwise unchanged.

The alveoli of the thyroid gland were dilated, lined by flattened cells, and contained a large amount of colloid. There were a few fat containing reticulum cells in the stroma. A branch of the thyroid vein contained serum with sufficient lipoid to stain it orange with sudan III.

There were no other important histologic observations in this case, except for a small amount of fat in the liver cells and a large amount in the suprarenal glands.

Anatomic Diagnosis.—The anatomic diagnosis was: lipoid nephrosis, fourth stage, with contraction; pseudochylous ascites and hydropericardium; atrophy of the myocardium, and increased lipoid content of the suprarenal cortex.

Comment.—The fourth stage of nephrosis is contraction. Rarely is it permitted to reach this stage, unhindered. The chronic metabolic disturbance leads to a profound visceral cachexia, as noted in our case in the premature brown atrophy of the heart at the age of 26. The atrophied and waterlogged tissues are susceptible to infection. Somewhere in the prolonged course of the ailment, the patient may be carried off by a pneumococcic peritonitis, an incidental infection, a superimposed glomerulonephritis or a myocardial failure. But, on rare occasions, as in this case, a pure nephrotic contraction is permitted to take place.

Because most of the rare cases described were in syphilitic patients, Munk termed the condition, "chronic syphilitic nephrosis with contraction." He scoffed at the suggestion of the mercury or arsenic being culpable. Indeed, he considered the only rational treatment in these cases to be active antisyphilitic therapy. The suspicion of syphilis was entertained in my case, but the patient did not enter the hospital until after a vigorous course of treatment, and his Wassermann reaction was then negative.

Histologically, the picture was strikingly different from other forms of contracted kidney. In nephritis, the inflammatory glomerular damage shuts off the function and the blood supply of the tubules. These disintegrate and are replaced by scar tissue, which contracts. In arteriosclerosis, the glomerular anemia produces the same result. In the severe tubular injury of the kidney damaged by corrosive sublimate, actual necrosis of the cells occurs and eventually scar replacement begins. In my case of lipoid nephrosis with contraction there were indeed glomerular and vascular changes. But they were neither inflammatory nor sclerotic in type and in no way comparable with the extreme contraction changes. There was no tubular necrosis, glomerular dam-

age or arteriosclerosis which could adequately account for it, yet the kidneys were severely contracted.

An explanation for this contraction one finds in the interstitial tissue itself. Several desmoplastic factors work hand in hand. In the early interstitial tissue changes, the histiocytes proliferate to take up the circulating lipoid and the lipoid from the slowly deteriorating epithelial tubular cells. They become swollen with singly refractile fats and with cholesterol. This swelling and proliferation of the histiocytes shuts off or narrows the lymph channels. The lymph stasis, in turn, induces further connective tissue proliferation, just as it does, for example, in filarial elephantiasis. Furthermore, the cholesterol is in itself desmoplastic. Injected into the peritoneal cavity, it induces the formation of a granulation tissue which soon becomes sclerotic; absorbed into the renal histiocytes, it does the same. Mechanically, also, the cholesterol droplets block the lymphatics and in this second way also contribute the extensive connective tissue proliferation.

As the tubules atrophy, they are seen to be widely separated by the increased and fat-laden interstitial tissue. The increase in connective tissue about the glomeruli produces pericapsular thickening, which should be separated from the intracapsular thickenings derived from organized crescents. This mechanically constricts the glomeruli as it shrinks, particularly involving the periglomerular capillary and the afferent arteriole. The glomerular blood supply is thereby reduced. Here and there, a glomerular capillary loop collapses, and part of the tuft loses all structural definition melting into a hyalinized strand. The glomerular epithelium is also damaged by the glomerulonephrosis, and may suffer secondarily from the tubular atrophy. These factors, together, proceed to partial or complete hyalinization of some of the glomeruli. This, in turn, then aggravates the tubular and interstitial changes.

The markedly increased interstitial connective tissue shrinks. As it shrinks, the kidneys contract. As they contract, the medium-sized blood vessels are rendered tortuous, and the tangential sections usually give a deceptive appearance of thickening. Thus without necrosis, inflammation or arteriolosclerosis does the nephrotic kidney contract.

The anatomic picture of nephrotic contraction is usually labeled "nephritis interstitialis chronica fibrosa multiplex," because in most cases the contraction changes are found in islands scattered between the less severely involved tissues. With few exceptions, the nephrotic contracted kidneys are described as granular. Only in an occasional case, such as mine, has such a kidney been described as almost perfectly smooth (a "glatte Schrumpfniere") with diffusely uniform atrophy and contraction. Why was this nephrotic contracted kidney smooth,

and others granular? How does it come about at times that in one kidney there can be granular patches of contraction, and smooth ones?

An answer to this question was offered shortly by an obvious case of primary contracted kidneys (malignant nephrosclerosis) in which one side of the kidney was found perfectly smooth and the other side perfectly granular. Death had occurred in uremia.

On microscopic examination of this kidney, one found that in the smooth-surfaced part, the main artery was so severely narrowed that the blood supply to the parenchyma was diffusely and severely impaired. The diffuse glomerular damage led to tubular atrophy and interstitial tissue proliferation. Shrinking of this caused contraction. The tubular atrophy was so severe that no regeneration took place, and the surface was smooth.

In the granular contracted part, the main artery was not so severely narrowed. The blood supply was somewhat less impaired. Enough blood passed through to the tubules so that some of them could regenerate, to compensate for those which had atrophied. These groups of regenerating tubuli lifted the contracted surface into fine granulations.

While it is therefore the shrinking of the proliferated interstitial tissue and to a small extent the parenchymatous atrophy which produces contraction, it is the regeneration of groups of less severely involved tubuli which produces granulation. In my case of "glatte Schrumpfniere," the tubular damage was so great that no power of regeneration was left to disturb by granule production, the smooth contraction of the interstitial tissue.

Even in the third stage of interstitial tissue changes, nephrosis begins to change from a simple metabolic disturbance to a real disease of the kidney. In the fourth stage of contraction, manifest renal insufficiency supervenes. True, comatose uremia does not appear, but the urea nitrogen and creatinine pile up in the blood, the carbon dioxide combining-power of the plasma sinks, the urine assumes a low fixed specific gravity and a severe uremia develops. That the blood pressure rises slightly, if at all, and that the heart does not hypertrophy are only results of the concomitant metabolic disturbance, which leads to a premature visceral cachexia and atrophy. Generalized arteriolar spasm or sclerosis are also lacking. But in many details the clinical picture may closely simulate that of chronic nephritis.

In particular, chronic nephritis with a marked nephrotic component may be clinically identical with true lipoid nephrosis. The same hypercholesterolemia, doubly refractile lipoiduria and reversed albumin-globulin ratio may be present. The blood pressure may be low in both and the cardiac hypertrophy slight. The gross anatomic appearance may be the same. Even histologically, the lipoid and interstitial changes may be identical; the differentiation can be made only by the

finding of the presence or the absence of inflammatory changes and by the marked disproportion between the glomerular and the tubulo-interstitial changes.

No wonder, then, that the careful clinician hesitates to make the differential diagnosis. Yet it is of some importance to do so, for the prognosis of nephrosis is considerably better than that of nephritis, and the treatment differs. The clinician complains therefore with justice that he cannot wait for the microscopic postmortem examination to make the diagnosis. As far as I have been able to find, there is only one clinical test that might be offered to help establish the diagnosis before death. This is the congo red test, which will be described in connection with case 3.

The nephrotic kidney is abnormally and specifically permeable to this dye. The nephrtic kidney, be its nephrotic component ever so marked, is not, it is claimed, permeable to it. Why this difference is not known. But different they are, for on applying this test, the urine of nephritis remains colorless, and the blood serum long stays pink; the urine of nephrosis, on the other hand, turns pink promptly, as the dye is rapidly discharged from the blood. Only this test might help to differentiate nephrosis from nephritis with a nephrotic "Einschlag." More work needs to be done with it.

The test has also proved of great value in detecting otherwise hidden amyloidoses. The difficulty of detecting amyloidosis before it is irreparably far advanced is well known. The ease with which even earlier stages may be obscured by other conditions, particularly by lipoid nephrosis, is exemplified by case 4.

LIPOID NEPHROSIS WITH AMYLOIDOSIS

CASE 3.—*History.*—A colored woman, 30 years old, had since the age of 17, from time to time, acute exacerbations of a so-called "chronic rheumatism" in her right shoulder. When she was 25 years old, during such an attack, the right shoulder was incised and curetted. It reopened spontaneously twice after that and discharged thick pus. The last time was two years before the examination, and during this attack she suffered a generalzed edema. She recovered shortly, however, and was discharged.

She was then apparently well until one month before her present entrance; at this time, she was operated on for some pelvic complaints. The fallopian tubes and ovaries were found buried in plastic adhesions, and were removed. The day after the operation, pain began in the left shoulder, and the face became swollen. The legs began to swell while the patient was still in bed, and then the abdomen. This attack was similar to that two years before, but instead of subsiding, it steadily became worse.

Physical Examination.—The patient finally reentered the hospital with severe edema of the entire body, and huge ascites which prevented accurate palpation of the liver and spleen. The heart was not enlarged. The blood pressure was 108 systolic and 76 diastolic.

The left shoulder was swollen, tender and painful, but not hot. Aspiration of it yielded thick, sterile pus. The muscles of the right shoulder were atrophic. Overlying them was the scar of the old arthrotomy.

Laboratory Examination.—The x-ray picture showed a destructive process in the head of both the left and the right humerus. The chest was clear. The leukocyte count was 6,500.

There was a severe albuminuria with many hyaline and granular casts, but no red blood cells. Doubly refractile lipoids were found in the urine. The total output was about 1,300 cc. per day with a specific gravity varying widely from 1.005 to 1.020. The Mosenthal test showed a good power of water concentration (specific gravity 1.022) and a low night urine (230 cc.).

Blood chemistry returned 10 mg. of urea nitrogen per hundred cubic centimeters and a cholesterol content of 400. The albumin content of the serum was severely reduced to the low level of 0.38 per cent, while the globulin maintained its normal average of 1.74 per cent.

Clinical Diagnosis.—The clinical diagnosis was: lipoid nephrosis or chronic nephritis and tuberculous arthritis of both shoulders.

Three days before her death, the patient suddenly felt a chill, followed by severe abdominal pain and the rising temperature of peritonitis. Paracentesis yielded 4,000 cc. of a green seropurulent fluid in which streptococci, but no pneumococci, were found.

Postmortem Examination.—There was a generalized anasarca. The abdominal cavity contained 1,000 cc. of yellowish-brown, cloudy fluid. The intestinal loops were agglutinated by loose, fibrinous adhesions. Their serosa showed injection in longitudinal, parallel bands.

The right pleural cavity contained 100 cc., the left 600 cc., of slightly cloudy fluid which compressed the left lower pulmonary lobe. There was a tuberculous primary nodule in the right lower pulmonary lobe. Otherwise, the lungs were clear.

A fluctuating swelling in the region of both shoulder joints was associated with an abnormal mobility of these joints. When the shoulder joints were opened, the joint surfaces were found separated by thick, green purulent material. The margins of the articular cartilage of both humeral heads were deeply eroded; their articulating surfaces were relatively intact.

The myocardium was grayish brown and friable. The heart weighed 235 Gm.

The liver was enlarged to 2,140 Gm.; its consistency was somewhat diminished. The cut surface was reddish brown, with light yellow patches and deep purple acinar markings. The spleen weighed 130 Gm. and was softened. Its pulp was deep grayish red, its trabeculae indistinct.

Both kidneys were markedly enlarged. The right weighed 323 Gm.; the left, 345. The capsule stripped easily, leaving a light yellowish-gray surface with numerous, pinpoint-sized brighter yellow areas. The consistency was slightly decreased. On cut surface, the cortex was 10 mm. wide and light yellow with pink to yellowish-white patches up to 1 mm. in diameter. The medulla was purplish gray.

Microscopic Examination.—Almost all the renal glomeruli were markedly enlarged, filling an entire high power field. The glomerular spaces were obliterated by the subendothelial deposit of a homogeneous azurophilic material. By specific stains (congo red or gentian violet) this material was shown to be amyloid.

There was no increased cellularity. On the contrary, many of the glomerular capillaries were narrowed, and in places obliterated by this deposit. However, many patent, blood-filled capillaries were still present in the enlarged glomeruli. Only a few glomeruli were somewhat smaller and almost completely obliterated by the amyloid. Occasional fine fat droplets were scattered through the cells of the tufts. A pericapsular thickening of connective tissue about each glomerulus was evident.

Two types of convoluted tubuli could be distinguished. One type had a relatively low epithelium with many fat droplets in the basal portion of the cells. The lumen of these tubules contained many casts and free round cells with pyknotic nuclei and cytoplasm stuffed by doubly refractile fat. These were the tubules of the first order, close to the glomeruli. The second type of tubules, farther away, belonging to the third order, was free from fat, but had large epithelial cells, filled with hyaline droplets.

The stroma was diffusely increased. It contained many groups of foamy cells, in which large amounts of doubly refracting fat were deposited. Besides these lipophages, it contained small accumulations of round cells. Amyloid was deposited beneath the finest capillaries of the stroma and in the walls of the arterioles and the smaller arteries.

In the liver, amyloid was found by specific stains in the walls of the arterioles and smaller arteries. Small lipoid droplets filled the liver cells in the periphery of the acini, but were restricted to the enlarged Kupffer cells in the central portions.

Amyloid was found also in the smaller arteries of the spleen and suprarenal glands. Lipoid granules were also found in the reticulum cells of the stroma of the pancreas.

Anatomic Diagnosis.—The anatomic diagnosis was: lipoid nephrosis with extensive amyloid infiltration of the kidneys; amyloidosis of the liver, spleen and suprarenal glands; chronic pyogenic arthritis of both shoulder joints; diffuse fibrinopurulent peritonitis (streptococcic); ascites and serofibrinous pleuritis; fatty changes of the liver, and anasarca.

Comment.—No suspicion of amyloidosis was entertained in this case until microscopic examination of the kidneys revealed it. It was appreciated that a chronic pyogenic arthritis would cause amyloidosis, but it might just as well produce a simple lipoid nephrosis without amyloid. Hepatic enlargement could also be completely accounted for by fatty changes without amyloid. Clinically there was nothing lacking to make it a simple, classic, irrefutable lipoid nephrosis. Every symptom, sign and laboratory observation of a pure lipoid nephrosis was present. Even at autopsy, the gross appearance indicated only the lipoid changes.

It was with some surprise, therefore, that on microscopic examination of the kidneys an extensive amyloidosis was unearthed. In addition there was also present every histologic requirement for a lipoid nephrosis. Similar cases of lipoid nephrosis completely obscuring clinically even an advanced amyloidosis have been reported by others (von Mogens [29]).

29. Mogens, N. von: Ueber die klinische Diagnose der Amyloidose mittels Kongorotinjektionen, München. med. Wchnschr. **75**:1883, 1928.

Pure amyloidosis may occur alone. In early stages, it causes no renal symptoms of its own. It rests indifferently under the basement membranes. Only when far advanced, does it lead to kidney damage. Pure lipoid nephrosis may occur alone, produce a typical clinical picture and even proceed to renal contraction without the slightest trace of amyloid.

Nephrosis and amyloidosis may occur together, but the two histologic pictures retain their independence. Since early amyloidosis yields no symptoms, the clinical picture of lipoid nephrosis with early or moderate amyloidosis is the same as that without it. Thus Fahr reports that in sixteen of nineteen cases of amyloidosis with marked edema, there was an associated lipoid nephrosis. Of eleven cases of symptomless amyloidosis, only three showed some lipoid changes; the rest, none. Advanced amyloidosis may, however, change the oliguria of nephrosis to polyuria, and it contributes to the process of nephrotic contraction. Therefore are contracted kidneys more common in lipoid nephrosis with amyloidosis than in lipoid nephrosis without it.

How to distinguish the two processes has been a problem. Lipoid nephrosis does not cause amyloidosis. Amyloidosis does not necessarily lead to lipoid nephrosis. For either condition may become far advanced without the other. When they appear together, the two are separate and distinct consequences of a common injury. Any focus of suppuration sends into the blood stream products of purulent destruction which are foreign bodies to the system. The repeated discharge of foreign proteins into the circulation leads to the deposition of amyloid (Jaffé [30]). The same focus of cellular destruction which causes this amyloidosis also sends into the circulation those toxic products which upset the lipoid-protein metabolism and induce lipoid nephrosis.

Yet the clinical differentiation is of great importance. It is essential to detect early amyloidosis even if obscured by lipoid nephrosis; for its discovery gives a different aspect to the prognosis and treatment in the case. Lipoid nephrosis is comparatively benign (Steinitz [31]). Most of the patients are alive long after the first symptoms appear. Amyloidosis gives to the case a much more grave prognosis. It bespeaks a hopeless devitalization of the patient by the toxins of prolonged suppuration. It contributes a serious element to renal damage.

Indeed, it was long considered that once amyloidosis developed, it was irreversible, and the patients died. This was only because our methods of detecting it were so crude that it could not be diagnosed

30. Jaffé, R. H.: Experimental Amyloidosis in Mice, Arch. Path. **2**:149 (Aug.) 1926.

31. Steinitz, H.: Zur Prognose der genuinen Nephrosen, Deutsche med. Wchnschr. **51**:1906, 1925.

until irreparably advanced. Bennhold [32] found that by applying the congo red test he could detect amyloidosis in its early stages, long before it gave any clinical symptoms. If this was then taken as an indication for medical treatment and the focus of suppuration was promptly dealt with, the patients recovered, and the amyloidosis gradually disappeared. Amyloidosis, if detected early, is not irreversible.

The congo red test has been used extensively in Europe. In the course of its application, it was found not only to be a sensitive test for early amyloidosis even when complicated by nephrosis, but to give a specific reaction in nephrosis which differentiated this disease even from chronic nephritis with a marked nephrotic component. I therefore tried it out in a few typical cases, to help introduce this valuable test into use in this country.

METHODS FOR CONGO RED TEST

Preparation of the Congo Red Solution.—Triple distilled water is sterilized twice at 15 pounds' (6.8 Kg.) pressure. The congo red is weighed out sterilly, and a 1 per cent solution made up. This is resterilized by heating for ten minutes to just below boiling. It is then filtered through a sterile funnel. To make sure it was harmless, 10 cc. of the 1 per cent solution was injected intravenously into a rabbit. There were no ill effects. Then doses of 1 cc., 2 cc. and finally 4 cc. were injected into normal persons. There were no ill results. The solution, so prepared and certified, if kept on ice, can be used for two days.

Application.—Bennhold's original technic is an accurate quantitative one. The injections are made before breakfast or some time after a meal, so that the serum shall not be too milky. Ten cubic centimeters of the 1 per cent solution is injected intravenously. At the end of four minutes, as soon as the dye has been evenly dispersed in the circulation, 5 cc. of blood is withdrawn by a second venipuncture. The patient's bladder is emptied, and he is given a glass of tea or water. At the end of sixty minutes, with care to avoid hemolysis, a second 5 cc. sample of blood is drawn, and another sample of urine is obtained.

Reading and Interpretation.—The serums are compared in an Autenrieth colorimeter. The serum of the four minute sample is pink and represents 100 per cent concentration of the dye. To make sure that the pink of the serum is not the result of hemolysis, it is necessary only to add one drop of concentrated hydrochloric acid to a portion of it. Normal serum gives a white precipitate. Pink serum gives a blue precipitate if its color is due to the dye, a brown one (hematin) if it is due to hemolyzed blood. During the course of an hour, the congo red is slowly excreted through the liver. Normally, at the end of sixty minutes, the serum is a slightly lighter pink; about 80 per cent of it is left. The samples of urine are both colorless.

In nephrosis, however, the kidneys are, for no known reason, abnormally permeable to the dye. By the end of one hour up to 60 per cent of it may be

32. Bennhold, H.: Ueber die Ausscheidung intravenös einverleibten Kongorotes bei den verschiedensten Erkrankungen, insbesondere bei Amyloidosis, Deutsches Arch. f. klin. Med. **142**:32, 1923.

lost, so that the second serum is much lighter in color than the first. The lost dye is found in the urine. While the first sample of urine is normally yellow, that voided at the end of an hour is pink. This pink urine of the congo red test indicates nephrosis. It does not appear in any other condition, not even in chronic nephritis with a nephrotic component.

In amyloidosis, the dye disappears from the blood stream with such great rapidity that from 60 to 100 per cent of it may be lost within the hour. The second serum becomes practically colorless. But the lost dye is not found in the urine. The urine remains colorless. The dye disappears because amyloid has a specific affinity for congo red. The amyloid, wherever it may be in the body, graps the congo red from the circulating blood.

Simplified Method.—To obviate the necessity of a colorimeter, Paunz, Nemeth,[33] Strasser[34] and later von Mogens tried various modifications of this technic. They planned to give such a suitable quantity of the dye that with any appreciable amyloidosis or nephrosis there would be enough change of color in an hour to be directly read by the naked eye. The method is otherwise the same as Bennhold's, but the reading is much simplified. The dose von Mogens employed was 0.08 cc. of the 1 per cent solution per kilogram of body weight. This is the method I used.

TABLE 1.—*Results with Congo-Red Test*

Condition	Serum 1	Serum 2	Urine 1	Urine 2
1.* Normal	Deep pink	Deep pink	Yellow	Yellow
2. Pulmonary tuberculosis (no amyloidosis)	Deep pink	Deep pink	Yellow	Yellow
3. Pott's disease (slight amyloidosis)	Deep pink	Slightly fainter pink	Yellow	Yellow
4.* Tuberculous arthritis (severe amyloidosis)	Deep pink	Colorless	Yellow	Yellow
5.* Chronic nephritis with nephrotic component	Deep pink	Deep pink	Yellow	Yellow
6.* True lipoid nephrosis	Deep pink	Faint pink	Yellow	Deep pink

A second case of lipoid nephrosis with amyloidosis has not offered itself yet for trial. Strasser[34] discussed the possibility and is also waiting for such a case. The investigators mentioned have all had excellent results with this test. Prepared under the directions given, it has never caused the slightest toxic symptoms. If several tests are done together, not much time is consumed. It is the only clinical test offered which may help to differentiate a true lipoid nephrosis from chronic nephritis with a marked nephrotic component, and which can detect an early amyloidosis before it is irreparable.

SUMMARY AND CONCLUSIONS

Pure lipoid nephrosis does exist. It is primarily not a kidney disease, but a disturbance in lipoid-protein metabolism, a "lipoid-protein

33. Nemeth, L.: Ueber den klinischen Wert des Nachweises der Amyloidose durch die Kongorotprobe, Klin. Wchnschr. **5**:1040, 1926.

34. Strasser, Ulrich: Zur klinischen Diagnose amyloider Veraenderungen mittels Kongorot, Wien. Arch. f. inn. Med. **14**:97, 1927; Die Kongorotprobe auf Amyloid bei nephrotischem Symptomenkomplex, Med. Klin. **25**:468, 1929.

diabetes." The kidneys are involved only because of their rôle as active excretory organs for the products of the disturbed metabolism. Renal changes start with hyperactivity of the renal epithelium. These proceed slowly to exhaustion atrophy and degeneration of the tubule cells. The sessile histiocytes of the renal stroma proliferate and take up lipoids from the blood stream and from the degenerated tubular epithelium. The proliferated interstitial tissue shrinks, constricting the glomeruli and contracting the kidneys. This shrinking produces a smooth renal contraction, a "glatte Schrumpfiniere." But if the tubules are not too severely damaged, some of them regenerate. This active regeneration renders the surface of the smoothly contracted kidney granular.

Not every renal lipoid infiltration is a lipoid nephrosis. True lipoid nephrosis is probably rare. Its histologic requirements are marked renal interstitial changes, as described, and lipoid involvement of the reticulum tissue all over the body. It is separated pathologically from chronic nephritis with a nephrotic component ("Einschlag") by the absence of inflammatory or arteriosclerotic changes and by the marked disproportion between the slight glomerular and vascular changes and the profound tubular and interstitial ones. Clinically, so far, the differentiation may be impossible, except that the congo red test may prove by many more trials to be reliable.

Amyloidosis and lipoid nephrosis are separate and distinct consequences of a common injurious agent. Amyloidosis when superimposed on lipoid nephrosis contributes to the renal damage and renders the prognosis grave. But each process may appear alone. Early amyloidosis gives no clinical warning of its progress. It can be detected before it is irreversibly advanced only by the use of the congo red test described.

Book Reviews

La hipertension arterial: Hipertonia arterial o hiperpiesis y los estados hypertensivos hipertonicos o de hiperpiesia. By doctor Mariano R. Castex. Prologo del doctor H. Vaquez. Pp. 590. Buenos Aires: Humberto Andreetta, 1929.

The preface of this book on arterial hypertension is written by Vaquez. The famous French clinician expresses admiration for the courage of the author in assembling the mass of data on hypertension. It must have taken enormous patience, effort and time to have collected what amounts to the world's literature on blood pressure. The citations are often lengthy and verbatim, adding considerable bulk to the volume but serving the purpose of quoting the authors so well as scarcely to require further reference to the original articles. Every section of this book begins with a complete review of the literature, even to the finest ramifications of the topic under discussion, and is then followed by the author's modestly expressed personal experience and critical considerations. As a result of this uniform procedure, there is a certain monotony.

The first part is devoted to the physiology of blood pressure. Of all the factors considered, the nervous system is given dominance as the regulator of normal, as well as of abnormal, arterial tension. The section on capillary and venous pressure is one of the rare weak spots, from the bibliographic aspect.

The general problem of hypertension, the older theories of pathogenesis and the clinical phases are considered in the second part. The compensatory or teleologic theory is decisively rejected. Hypertension is always pathologic, according to the author, and should be combated as early as possible. The vascular crises are well reviewed. The capillaries are said to play no rôle in the genesis of hypertension. The symptoms are determined by the hypertension per se, by the causal factors and the coordinated effects they produce and by the somatic and psychic make-up of the individual. As to treatment, the Hippocratic principle "confluxio una, conspiratio una, consententia omnium" is wisely chosen as the slogan. The author commits himself frankly on the great host of medicaments and physiotherapeutic procedures and expresses no enthusiasm for such regimens as the calcium-atropine therapy of Kylin. This is one of the best chapters in the book, especially because of its emphasis on the consideration of the complete picture of the patient and his environment. The details of treatment are clearly related to the various indications. However, the recommendation to remove all foci of infection as an absolute routine indicates that this wave of destructive enthusiasm has already gripped the South American continent. Furthermore, the author's insistence on the etiologic and pathogenic diagnosis of hypertension before treatment is instituted must be accepted philosophically in view of the bleak situation in regard to such diagnosis.

As to pathogenesis, the author has a message to deliver and he dwells long and hard on it. Hypertension is largely of nervous origin, in turn either central or reflex. The hypothalamus is the center of the plot and this is influenced from above in psychogenic hypertension, or directly by toxic, inflammatory, degenerative or mechanical insults, or reflexly from the peripheral nervous system. Hence, all one has to do is to decide which one of these influences is acting on the hypothalamic vasomotor centers (the existence of which not all physiologists admit as yet) and thus make a topographic, pathogenic diagnosis. What could be simpler? Unfortunately, the author admits that many factors often cooperate to make such diagnosis difficult. He shows good judgment in throwing out salt, blood cholesterol, normal protein intake and tobacco as of any importance, but he retains alcohol on the usual flimsy evidence. Toxic hypertension is simply ascribed to focal infection — and there are many foci.

In the third part the various types of hypertension are developed from the clinical point of view, with the foregoing pathogenic scheme of Kahler as the background. Paroxysmal hypertension is well discussed. Everywhere causal therapy is advised; everywhere the stimulation of the diencephalic center is the cause of the hypertension. Much space is devoted to hypertension in cardiovascular disease, with emphasis on the work of the Hering school. The important problem of the renal causation of hypertension is exhaustively treated and finally the entire subject wound up with the opinion that diffuse renal disease and hypertension are autonomous but coordinated phenomena, having a common causal factor. The treatment is simple: operative, chemotherapeutic, foreign protein, serums, vaccines, etc. Early tonsillectomy is recommended, except in full-blown uremia. Malignant nephrosclerosis is considered in the same general fashion. Uremia is caused by a toxemia from focal infection and is characterized by a chaos in protein metabolism, which is due to a general tissue disturbance or to an effect on the metabolic centers in the diencephalon. The theory of the vegetative centers is developed in all its German massiveness of detail so that every possible clinical variation is explained on the involvement of different centers for partial functions. One begins to wish for a judicious regulator of all these regulatory centers in such close quarters.

The author is a great believer in enterogenous toxemia, and presents his side of the question without bothering about the opposition. If a vegetarian is reported to have developed hypertension, extra-intestinal factors must have been at work. Digestive toxemia may cause hypertension by the usual toxic, mechanical or reflex routes. The liver helps to detoxicate. In the functional types, vaccine and foreign protein therapy are effective.

The association of hypertension with diabetes, gout, obesity, hypercholesterolemia, pregnancy, diseases of the ductless glands, etc., is uniformly explained by the involvement of adjacent diencephalic vegetative centers. The permutations and combinations obviously are infinite and satisfying to the author.

The result achieved in this book is a creditable encyclopedic bibliography on blood pressure, but no great light is shed on the difficult field surveyed. There is an open challenge to all who read between the lines of the 590 pages — to debunk the diencephalon or to establish it scientifically as an absolute oligarchy, before more clinicians are led astray by their physiologic or clinical colleagues.

EDEMA AND ITS TREATMENT. By HERMAN ELWYN, M.D., Assistant Visiting Physician, Gouverneur Hospital New York. Price, $2.50. New York: The Macmillan Company, 1929.

This monograph represents a rather violent reaction to the Starling-Epstein theory of edema and the whole concept of the rôle of mechanical forces in the fluid exchange between the blood and the tissues. Following the school of Kraus and Zondek, the author presents the evidence and the arguments in favor of a regulatory center for water balance situated in the hypothalamus. This center acts through nervous pathways and by means of the "hormone" of the intermediate and posterior lobes of the hypophysis on the "constellation of electrolytes" in the cells of the various organs, tissues and vascular structures involved in water balance. The whole purpose of this regulation is to keep the volume of the blood plasma constant. The chief stimulus to the center is an increase in, or a threat to increase, the water content of the blood. Oliguria, of acute nephritic or cardiac origin, is the most important stimulus. The regulatory center responds by sending out nervous impulses or the "hormone" to decrease the rate of movement of water from the tissues to the blood; hence the edema in cardiac failure and in acute glomerulonephritis. The edema in nephrotic renal disease, and in war-edema, is due to a decreased intensity of function on the part of the water center and other centers around the third ventricle. This depression is presumably secondary to the general state of undernutrition. Edema, in general, is compensatory to prevent an increase of the blood volume. Oliguria in nephrosis is compensatory to prevent loss of protein.

Diabetes insipidus represents increased function of the water center with resulting increase in the rate of movement of water throughout the entire system responsible for the maintenance of the water balance. The action of posterior pituitary extract as an antidiuretic is taken as evidence of the existence of a true hormone elaborated by the hypophysis in response to stimuli from the regulating hypothalamic center. A similar argument, of course, would make "hormones" out of digitalis, quinidine and many other drugs, because they tend to restore some abnormal function to the normal state.

The author does not explain why the regulating center is unable to affect the rate of movement of water from the blood into the tissues and thus prevent edema. He makes the rather fatal assumption of identity in action between such widely divergent systems as frog's skin, pig's intestinal wall and vascular capillary membranes toward the passage of fluids through them. The Donnan equilibrium between serum and edema fluid, whether in vivo or in vitro, is not considered. The lack of obvious disturbances in water balance in completely sympathectomized cats is also not mentioned. The weak experimental evidence for the existence of hypothalamic centers for partial metabolic functions is fortified by verbally lucid teleologic reasoning, the glittering haze of which adequately obscures the numerous pure assumptions. Constant repetition and well timed emphasis lend a convincing background to the thesis that edema is always a disturbance in central regulation and that it is always to be explained by decrease in the rate of movement of water from the tissues to the blood, the opposite movement apparently being beyond the control of the center. The mechanism of thirst is fitted into the scheme somehow.

The difficulty with the whole explanation of edema on the foregoing basis is that all general edemas are explained alike, when clinical and experimental facts point to wide differences in the pathogenesis of edema and in the nature of the edema fluid. Furthermore, as Volhard has stated in a review of this book (*Zentralbl. f. inn. Med.* **50**:1042, 1929), the author fails to consider those states of edema in which no disproportion can be demonstrated between the rate of inflow and the rate of output of water. The lack of edema in prolonged anuria and in many cases of fatal renal insufficiency with oliguria is also not explained. Volhard maintains, as he always has, that oliguria is usually the result and not the cause of edema. Elwyn does not indicate why rigid restriction of salt and water intake is in itself entirely inadequate in the management of many cases of edema.

In the chapters on treatment the usual principles are laid down and the various diuretics discussed along orthodox lines. Parathyroid hormone is not mentioned.

The good features of this monograph are the excellent review of the available, chiefly German, literature on the "vegetative system" the detailed description of the clinical studies on war-edema, the discussion of the water depots in the body and their response to various experimental procedures and, above all, the unerring clarity of diction and simplicity of style so characteristic of all of the publications of Elwyn.

To the clinician searching for an answer to the complex problem of the pathogenesis of the various clinical types of edema this monograph will give little consolation, unless the credulity of the reader outweighs his critical acumen. To the physiologist who is sufficiently irritated by the one-sided point of view developed by the author, the book should function as an excellent cerebral stimulant and lead to a critical experimental attack on the vegetative centers. So far, the speculation has completely outdistanced the facts.

THE ESSENTIALS OF MEDICAL DIAGNOSIS. By SIR THOMAS HORDER, K.C.V.O., M.D., F.R.C.P. (LONDON), and A. E. GOW, M.D., F.R.C.P. (LONDON). Price, $5.00. Pp. 682. New York: William Wood & Company, 1929.

The preface to this book gives an excellent discussion of the problems involved in the teaching of beginning clinical medicine and physical diagnosis. It is emphasized by the authors that differential diagnosis must be thought of very early in

the examination of the patient, and the entire book is developed along this idea. The book is divided according to systems, beginning with the nervous system, to which at least one fourth of the entire space is devoted, as might be expected in an English text. Then come the cardiovascular system, the respiratory system, the digestive system, the urinary system, the blood and blood-forming organs, the joints, the ductless glands, the skin and its appendages and a short chapter on pyrexia. Emphasis is placed on all practical clinical points, and little space is given to theoretical aspects. The arrangement of the book is good, in which the discussion proceeds from anatomy, through physiology, physical observations, the clinical diseases and differential diagnosis. Some of the simpler laboratory methods are included but are necessarily brief. The illustrations are much fewer than in American textbooks, and are almost entirely anatomic or x-ray pictures, but are all to the point. There is also a good index. For its size the book is excellent and will prove particularly valuable to those of a clinical turn of mind.

THREE MINUTE MEDICINE. A SERIES OF BRIEF ESSAYS ON POPULAR MEDICINE. By LOUIS R. EFFLER, A.M., M.D., Director of Education, The Toledo Academy of Medicine, 1927-1928. Pp. 459. Boston: Richard G. Badger, 1929.

This volume of 200 short, pointed sketches on all possible medical topics accomplishes successfully what it was meant to be — a series of brief essays on popular medicine. As the author states in the preface, these essays were a reply to the open challenge of the *Saturday Evening Post,* that organized medicine should come down to "simple, racy English" and inform the public. The public which read these essays in the *Toledo Times* have been informed well on a great many items of historical interest in medicine and related sciences. It is refreshing to note the absence of specific diagnostic and therapeutic advice with which the daily medical columns are so full these days. To the busy practitioner and the medical student these essays furnish an easy and appetizing introduction into medical history. To the publicity committees of medical societies, the organization that made these essays possible could well serve as an excellent precedent. The book is well printed and free from errors except for a few amusing slips in the essay on Nobel Prize winners. Every physician's waiting room should have a copy.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG: II. TAGUNG. HERAUSGEGEBEN VON PROF. DR. BRUNO KISCH, KÖLN. Price, 15 marks. Pp. 177. Dresden: Theodor Steinkopff, 1929.

The proceedings of the second meeting of the German Society for the Study of the Circulation seem to justify its establishment as a separate group with not only a specialized interest in a limited field, but broad contacts in many related fields because of the universal importance of the circulation in health and disease. For these reasons the various articles should prove of interest to the general internist, the cardiologist and the physiologist. Thus, there are papers on arteriosclerosis and old age, vascular damage by irradiated ergosterol, the cardiac output in hypertension, effects on blood pressure of obstruction of the external carotids in rabbits, rhythmic volume changes of vascular origin in the rabbit's ear, the physical registration of heart murmurs, the pathogenesis and treatment of edema, historical review of the use of digitalis as a diuretic, to mention only the most representative topics. This publication is a fitting addition to the well known *Zeitschrift für Kreislaufforschung.*

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1919
Vol
36
No 1

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